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Dimethoate: Position Document 4

(U.S.) Environmental Protection Agency
Arlington, VA

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U.S. Department of Commerce
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DIMETHOATE: POSITION DOCUMENT 4

Dimethoate Support Team
December 1980

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Dimethoate PD 4

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ENVIRONMENTAL PROTECTION AGENCY

[OPP]

PESTICIDE PRODUCTS CONTAINING DIMETHOATE

FINAL NOTICE OF DETERMINATION CONCLUDING REBUTTABLE PRESUMPTION AGAINST REGISTRATION AND CONTINUED REGISTRATION

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This Notice provides the Dimethoate Position Document 4 supporting the Notice of Intent to Cancel Registrations and Deny Applications for Registration for Pesticide Products Containing Dimethoate, which is published elsewhere in this issue of the FEDERAL REGISTER. Position Document 4 represents the final stage of the Agency's review of this chemical under the Rebuttable Presumption Against Registration Process. The Notice of Intent to Cancel Registrations and Deny Applications for Registration of Pesticide Products Containing Dimethoate describes the procedures for challenging the regulatory actions taken by the Agency concerning dimethoate.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. INTRODUCTION

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (7 U.S.C. 136 et seq.), the Environmental Protection Agency (EPA or "the Agency") regulates all pesticide products. Section 6(b) of FIFRA authorizes the Administrator of EPA to issue a notice of intent (1) to cancel the registration or (2) to change the classification of a pesticide product, if in his judgment either the pesticide or its labeling "does not comply with the provisions of (FIFRA) or, when used in accordance with widespread and commonly recognized practice, generally causes unreasonable adverse effects on the environment...." FIFRA, section 3(c)(6), authorizes the Administrator to deny any application for pesticide registration which does not meet the statutory standards for registration.

To implement its authorized functions, the Agency has designed the Rebuttable Presumption Against Registration (RPAR) process (described in 40 CFR 162.11), which involves gathering data on the risks and benefits associated with the use of suspect pesticides. By allowing all interested parties to participate by submitting information, the process enables EPA to make balanced decisions concerning problem pesticides.

The Agency published an RPAR notice in the FEDERAL REGISTER of September 12, 1977 (42 FR 45086) for all pesticide products containing dimethoate, an organophosphate insecticide and acaricide, thereby initiating the Agency's public review of the risks and benefits of dimethoate. The RPAR notice cited three risk criteria which dimethoate had met or exceeded. These three risk criteria were oncogenic effects in test animals (40 CFR 162.11(a)(3)(ii)(A)), mutagenic effects (multi-test evidence) (40 CFR 162.11(a)(3)(ii)(A)), and reproductive and fetotoxic effects in test animals (40 CFR 162.11(a)(3)(ii)(B)). A detailed Position Document 1 accompanied the September 12, 1977 notice.

The Agency issued a Preliminary Notice of Determination concluding the Rebuttable Presumption Against Registration of Pesticide Products containing Dimethoate and announced the availability of Position Document 2/3 in the FEDERAL REGISTER of November 19, 1979 (44 FR 66558). In Position Document 2/3, the Agency analyzed the rebuttals it received in response to the original RPAR notice, presented its analysis of both risks and benefits associated with the uses of dimethoate, and proposed a decision to conclude the RPAR process.

The Agency determined, in PD 2/3, that the information submitted to rebut the risk criteria for oncogenicity, mutagenicity, and reproductive and fetotoxic effects was insufficient to overcome the presumption against dimethoate for these effects. In addition the Agency received new teratogenic data, unavailable when PD 1 was issued, indicating that dimethoate posed a potential teratogenic hazard. This new information was presented and evaluated in PD 2/3 and the Agency concluded in PD 2/3 that teratogenicity was an additional risk of concern for dimethoate.

In the Preliminary Notice of Determination, the Agency determined that the risks arising from certain uses of dimethoate are greater than the benefits of those uses, unless risks are reduced by modifying certain terms and conditions of registration. The Agency determined that these modifications would significantly reduce risk without significantly impacting on the benefits of the uses.

The modifications to the terms and conditions of registration of dimethoate products proposed by the Agency in the Preliminary Notice of Determination included:

(1) Cancellation of dust formulations.

(2) Label changes to require the use of protective clothing and respirators.

(3) Label changes to require automatic flagging for aerial application.

(4) Label changes to prohibit air blast application on citrus, pome fruits, and pecans.

(5) Label changes to include a warning to female workers, using air blast equipment, of the potential teratogenic effects of dimethoate.

In addition, the Agency determined that registrants must submit data in the areas of oncogenicity, mutagenicity, delayed neurotoxicity, and applicator exposure pursuant to FIFRA sections 3(c)(2)(B).

FIFRA requires the Agency to submit notices issued pursuant to section 6 to the Secretary of Agriculture for comment and to provide the Secretary of Agriculture with an analysis of the impact of the proposed action on the agricultural economy under section 6(b). The statute also requires the Administrator to submit notices issued pursuant to section 6 to a Scientific Advisory Panel (SAP) for comment on the impact of the proposed action on health and the environment, at the same time and under the same procedures as those described for review by the Secretary of Agriculture under section 25(d).

Although not required to do so under the statute, the Agency decided that it is consistent with the general theme of the RPAR process and the Agency's overall policy of open decision-making to afford registrants and other interested persons an opportunity to comment on the bases for the proposed action during the time that the proposed action is under review by the Secretary of Agriculture and the SAP. Accordingly, the Preliminary Notice and PD 2/3 were made available to registrants and other interested persons at the time the decision documents were transmitted for formal external review. The Preliminary Notice was published in the FEDERAL REGISTER; interested persons were notified that PD 2/3 was available through publication of a Notice of Availability in the FEDERAL REGISTER. Registrants and other interested persons were allowed the same period of time to comment, 30 days, that the statute provides for receipt of comments from the Secretary of Agriculture and the SAP.

The Agency received comments from thirteen (13) parties, including the USDA and the SAP, in response to the notice of November 19, 1979. The comments are addressed and analyzed in Chapter II of this document. Chapter III summarizes the Agency's final determination concerning pesticide products containing dimethoate. SAP and USDA's responses are reproduced in their entirety at the end of this chapter. All comments are available for review in the public file located in the Document Control Office, Rm. E-447, 401 M St., S.W., Washington, D.C. 20460.

FIFRA SCIENTIFIC ADVISORY PANEL

REVIEW OF PRELIMINARY NOTICE OF DETERMINATION CONCLUDING THE REBUTTABLE PRESUMPTION AGAINST REGISTRATION (RPAR) OF PRODUCTS CONTAINING DIMETHOATE

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel has completed review of plans by the Environmental Protection Agency (EPA) for initiation of regulatory action on dimethoate pesticide products pursuant to section 6(b)(1) of FIFRA, as amended. The review was conducted during open meetings held in Arlington, Virginia, during the periods November 29, 1979, and January 17-18, 1980.

Maximum public participation was encouraged for the review. FEDERAL REGISTER notices of Panel meetings concerned with the review of dimethoate were published on November 14, 1979 and November 27, 1979. In addition, telephonic calls and special mailings were sent to members of the general public who had previously expressed an interest in activities of the Panel. Written and oral statements

(page 7a follows)

were received from EPA technical staff and from representatives of the American Cyanamid Company. In addition, oral comments were received from Mr. Harold Alfred of the Pesticide Impact Assessment Program, University of California. Informal comments were also received from Mr. Harold M. Collins of the National Agricultural Aviation Association.

The Panel wishes to recognize the excellent support provided by the Agency during review of dimethoate. The superb presentation of the Agency position on dimethoate by Ms. Marcia Williams, Mr. William Waugh, and other EPA technical staff enabled the Panel to concentrate on central issues and avoid lost time from problems of communication. Additionally, the Panel wishes to commend the Agency for exhibiting an excellent spirit of cooperation in making available relevant references and background data on dimethoate in advance of the meeting.

In consideration of all matters brought out during the meeting and careful review of all documents submitted by the Agency and other parties, the Panel unanimously submits the following report.

Panel Position on Dimethoate

Question 1. What is the significance of wavy ribs in teratology studies such as those conducted by Khera (unpublished)? It has been noted that these effects (wavy ribs) are often observed when the embryotoxic or fetotoxic dose is approached. Are wavy ribs a true teratogenic effect?

Answer. The Panel is unable to confirm that wavy ribs are a true teratogenic effect. Additionally, the Panel is unable to assess the significance of wavy ribs in studies conducted by Khera. Appropriate scientific data was not presented to the Panel for proper assessment of the topics outlined in number 1.

Question 2. What is the significance of polydactyly observed by Khera (unpublished)?

Answer. The significance of polydactyly cannot be properly assessed. The Panel is unaware of data which clearly relates

(page 8a follows)

the phenomenon of polydactyly as a dose-related toxicological manifestation which is well documented in the literature. In Khera's study it is impossible to determine whether polydactyly was an effect attributable to the agent or whether it was a background effect.

Question 3. In calculating the dietary exposure for the general population, the Agency assumed dimethoate residues to be present at tolerance levels. Tolerance levels were used because actual residue data were not available. The Agency then added this dietary exposure to anticipated occupational exposure to arrive at total applicator exposure. The Agency noted, however, that the oral exposure component, based on residues at tolerance levels, was in many cases greater than the occupational component and that the exposure figures for occupational exposure (without the dietary component) most closely approximated actual exposure. Was the Agency correct in its conclusion that applicator exposure, without oral exposure, most closely approximates actual applicator exposure? Given the available data, can the SAP propose another method of estimating applicator exposure for dimethoate?

Answer. The Panel could not adequately respond to all the facets of this question because of time constraints during the meeting. However, several possible approaches for better definition of human exposure were suggested. In general, the Panel agrees with the approach utilized by the Agency, but wishes to point out that in view of the biodegradability of dimethoate it is unlikely that the dietary level for this compound will approach tolerance levels. Additionally, the Panel recommends that appropriate field human monitoring studies be conducted to determine applicator exposure levels. Such studies are technically feasible and should be considered as the best means to characterize potential hazards in humans.

(page 9a follows)

Question 4. Does the SAP agree with the Agency's conclusion concerning the mutagenic risk from dimethoate?

Answer. Yes! The Panel concurs with the Agency that the mutagenic risk is low and that strong regulatory action is not warranted.

Question 5. Does the SAP agree that an additional oncogenicity study is required to answer the question concerning the oncogenic potential of dimethoate?

Answer. No! The Agency's proposal to require an additional oncogenicity study because of a study done abroad which is not interpretable does not seem to be a valid undertaking. The Panel is of the opinion that the NCI bioassay study was a valid test for the oncogenic potential of dimethoate. This is reinforced by the fact that dimethoate is an organophosphorus compound and that this class of pesticides are not known to be carcinogenic. Although the NCI study had flaws, the problem is that there is no such thing as a completely satisfactory test. Every test is flawed. It is a question of degree. The Panel does not believe that the NCI study was flawed to the point where it is of no value in regulatory action. This position was also taken by the Carcinogen Assessment Group (CAG) of the Agency.

Proposed Regulatory Action

The Panel concurs with the Agency's proposed regulatory action on dimethoate except as specifically noted below.

Exception 1. Prohibiition of the conventional use of human flaggers to mark swaths in aerial spraying and associated requirement for use of automatic flagging devices.

Panel comment. The Panel rejects this proposal on the basis that insufficient research has been accomplished to illustrate that the technique would be an effective regulatory procedure to reduce risks to man and the environment. To institute such a requirement across the board without determining the limitations of the procedure in various agricultural situations would appear to

(page 10a follows)

be inadvisable. The Panel recognizes the potential usefulness of such devices, but recommends that the Agency not make their use an absolute requirement until appropriate research has been completed to ensure that such devices are practical tools for reducing risks in spray applications. Additionally, the Panel encourages the Agency to promote research on flagging devices to expedite their development and availability to farmers.

Exception 2. Agency proposal to preclude use of air-blast equipment on citrus, pecans, and pome fruits.

Panel comment. The Panel does not support this proposal on the basis that appropriate data is lacking to adequately compare applicator exposure from use of air-blast equipment with exposure resulting from use of oscillating boom type sprayers. Additionally, the Panel is aware that a high number of farmers prefer the use of air-blast equipment and if dimethoate is not available then it is likely that substitute pesticides which may be more hazardous may be selected for use in air-blast equipment. Testimony was given by a representative from the State of California relative to planned research with dimethoate in the near future to assess applicator exposure from air-blast equipment in comparison with oscillating boom type sprayers. The Panel requested that his research plans to be expanded to ensure examination of urine samples to gain insight on possible absorption of pesticides by applicators. This will provide data not only on the agent, but also the mechanism of application.

It is important to emphasize that dimethoate is a valuable pesticide component of integrated pest management (IPM) programs for citrus insect pests and that such programs are almost totally based around the use of air-blast equipment to apply reduced dosages and selective coverage.

Additional Testing Requirements

The Panel concurs with the Agency's position relative to additional testing requirements with the following specific exceptions and comments.

(page 11a follows)

Exception 1. Oncogenicity testing--The panel considers the National Cancer Institute study on dimethoate to be a valid assessment of the oncogenic potential of dimethoate. Additional studies are not considered essential.

Exception 2. Mutagenicity testing--The Panel concurs that additional mutagenicity testing is needed to properly assess the mutagenic potential of dimethoate. However, to ensure appropriate assessment the Panel recommends that mutagenic assays be conducted in accordance with recommendations previously submitted by the Panel to the Agency (May 31, 1978; Review of Proposed Rulemaking on Subpart F, Guidelines for Registering Pesticides in the United States). Additionally, the Panel suggests that the Agency follow the recommendation previously submitted by the Panel on tests to assess the potential for spindle effects (November 30, 1979 - Review of FIFRA section 6(b)(1) action on Benomyl and Thiophonate-methyl). The Panel also recommends consideration of the use of bone marrow derived cells in assays for spindle effects.

Exception 3. Delayed Neurotoxicity Studies--The Panel requests the Agency reevaluate the need for additional delayed neurotoxicity studies in view of research reported by T.B. Gaines 1969, entitled "Acute Toxicity of Pesticides" (Toxicology and Applied Pharmacology Vol. 14, 515-534). No paralysis was observed by Dr. Gaines in tests conducted with dimethoate.

Exception 4. Reproductive Tests--The Panel recommends that the Agency require additional reproductive tests on dimethoate. The Panel notes positive effects in two studies on reproduction implying the possibility of effects on males. Therefore, we suggest that the Agency require a reproductive test to determine dose-response effects on females (e.g., prevalence of pregnancy, pre and post implantation loss, survival and growth of young, etc.) and on males (e.g., spermatogenesis, seminal vesicle size, etc.).

DATE: February 7, 1980

FOR THE CHAIRMAN:

H. Wade Fowler, Jr., Ph.D.
Executive Secretary,
FIFRA Scientific Advisory Panel

U.S. DEPARTMENT OF AGRICULTURE COMMENTS

U.S. Department of Agriculture
Office of Environmental Quality
Washington, D.C. 20250

December 12, 1979

Mr. Edwin L. Johnson,
Deputy Assitant Adminstrator
for Pesticide Programs
U.S. Environmental Protection Agency
Washington, D.C. 20460.

Dear Mr. Johnson:

This is in response to your letter of November 8, forwarding the U.S. Environmental Protection Agency's (EPA) preliminary notice of determination concluding the rebuttable presumption against registration (RPAR) and the proposed notice of intent to cancel and/or modify the terms and conditions of registration of pesticide products containing dimethoate.

After interacting with EPA in the development of the biological, economic, and exposure information on dimethoate, we are pleased to review and comment on the preliminary notice of determination and the accompanying position document.

We concur with the decision to continue registration of dimethoate on field crops, grains, grapes, certain minor and/or specialty crops, livestock premises, forest seed orchards, nurseries, ornamentals, vegetables, and for fly control. We also agree with the decision to cancel registrations for use in dust formulations.

The USDA supports the proposed modification of labeling to include statements requiring protective clothing and equipment for application. This action is in concert with the USDA/EPA joint publication, "Apply Pesticides Correctly, a Guide for Commercial Applicators."

With regards to the proposed requirement for automatic flagging when dimethoate is aerially applied, we encourage EPA to maintain the full range of options to minimize exposure. This could continue the registrations and might involve label statements requiring protective clothing and equipment to minimize exposure flaggers may experience. We feel that studies should be done to indicate actual exposure to dimethoate by all workers in the aerial application process.

We also have reservations regarding the cancellation of dimethoate use on citrus, pome fruits and pecans when it is applied by air blast equipment. Growers have indicated that equipment of this nature is essential for adequate application to these commodities. Otherwise, more frequent, less effective applications would be required. The general term, "air blast equipment", needs a more precise definition in fully interpreting this regulatory option. We are prepared to cooperate with EPA to develop directions to provide for minimal exposure in these situations.

Regarding the warning to female workers, we believe that all persons including, and perhaps especially, those who are pregnant should always endeavor to avoid or reduce exposure to all pesticides. If EPA wishes to alert female workers using air blast equipment of possible hazards resulting from exposure to dimethoate during pregnancy, we suggest that a more direct warning such as "Pregnant women should avoid exposure" would be more effective.

We are dedicated to the mutual resolution of issues concerning the health of farm workers and the general public as well as issues affecting crop production and the environment.

Sincerely,

Barry R. Flamm,
Director.

II. ANALYSIS OF COMMENTS

In response to the issuance of the Preliminary Notice of Determination and Position Document 2/3 on November 10, 1979, and the publication in the FEDERAL REGISTER of November 19, 1979 (44 FR 66558) of a Notice of Availability for Position Document 2/3, the Agency received comments from the Secretary of Agriculture, the SAP, and 11 other concerned individuals and organizations. These comments are organized by topic and discussed in this section. Except as discussed, the Agency has not changed any other aspect of its analysis presented in Position Document 2/3.

A. Comments Relating to Risk

1. Summary of the Agency's Risk Position in PD 2/3. The Agency's qualitative and quantitative risk assessment is based on its evaluation of the hazard of dimethoate in conjunction with a best estimate of the potential for human and environmental exposure.

The potential for human and environmental exposure to dimethoate was derived from available data and assumptions about work place practices, current agricultural practices, dietary habits, body weight, breathing rates, dermal exposure, similarity of application techniques, etc. The exposure figures obtained represent the Agency's best estimate of the exposure potential of dimethoate. Although there are uncertainties in these estimates, they permit a rough calculation of risk to the population at large and population subgroups, such as applicators or flaggers, with specific exposure potential. They also permit comparison of risk from dimethoate with that posed by other pesticides which are used as alternatives to dimethoate.

The dimethoate RPAR was based on information indicating that dimethoate posed the following risks to humans: (1) oncogenicity, (2) mutagenicity, and (3) reproductive and fetotoxic effects.

In Position Document 2/3 the Agency determined that the information submitted to rebut the risk criteria for oncogenicity was insufficient to overcome the presumption against dimethoate for this effect. However, the Agency concluded, based on a re-analysis of the studies involved and the rebuttal comments, that the weight of evidence for dimethoate's carcinogenicity is only suggestive, and that the evidence warrants further studies.

The Agency also determined that the rebuttal submissions were insufficient to remove the Agency's concern that dimethoate poses the risks of reproductive and fetotoxic effects to humans. In addition, new teratogenic data (Khera, undated), unavailable when the RPAR was issued, were submitted. These data indicate the potential of dimethoate to produce teratogenic effects.

The Agency further determined that the rebuttals and additional information submitted did not invalidate the mutagenicity risk presumption. However, the Agency concluded that the risk appears to be low and that additional test data are necessary to evaluate the quantitative mutagenic risk of this compound.

The Agency received comments concerning delayed neurotoxicity and the synergism of dimethoate with other pesticides, and concluded that there is insufficient evidence to indicate that dimethoate meets or exceeds the risk criteria enumerated in 40 CFR 162.11 for these effects, but that additional information concerning dimethoate's ability to induce delayed neurotoxicity must be generated.

The Agency determined that the principal risks of oncogenicity, mutagenicity, and reproductive and fetotoxic, and teratogenic effects are posed to applicators, who may be exposed to dimethoate before or during application through both inhalation of and dermal contact with the pesticide. The greatest risk to applicators is incurred by (1) the ground application of dust formulations on grapes, and (2) air blast spraying of citrus, pecans, and pome fruits.

2. Oncogenicity Risk--a. Summary of Laboratory Animal Studies Cited in PD 1--i. Gibel et al., 1973. Gibel et al. (1973) studied the effects of dimethoate on 10-week-old Wistar rats of both sexes. Forty animals per group were employed in the study. Fresh solutions of dimethoate

were made at the time of administration to limit hydrolysis. The compound was given twice weekly by gavage at 5, 15, and 30 mg/kg dose levels. One other group of animals was given 15 mg/kg intra-muscularly.

Animals were weighed at regular intervals. Only the animals that lived 3 months in the study and showed no post mortem changes were examined histologically. Blood and bone marrow were also examined.

Treated animals showed strong hyperplasis of the blood forming parenchyma of the bone marrow involving erythropoesis, granulopesis, and megakaryopoesis. Nonbony myeloid metaplasia was seen primarily in the liver and spleen in 59 percent of the treated animals. In addition, granulocytosis was found in 22 percent of the animals.

There was a significant increase in the incidence of benign and malignant tumors among treated animals at the 30 mg/kg dose level for oral administration and at the 15 mg/kg dose level for intra-muscular administration. In addition, there was a significant linear trend ($p<0.01$) for the oral route. (See Table 1).

TABLE 1 - Incidence of tumors in rats treated with dimethoate

Dose milligrams per kilogram	Route	Average survival (days)	Benign Tumors	Malignant Tumors	p values
0	oral	473	3/36	0/36	-
5	oral	518	7/26	2/26	-
15	oral	511	5/25	3/25	-
30	oral	627	2/25	4/25[a]	0.0132
0	Intra-muscular	711	4/35	0/35	-
15	Intra-muscular	570	5/30	6/30[b]	0.0072

[a] 1 liver sarcoma, 1 malignant reticulosis, and 2 sarcomas of the spleen.

[b] 1 sarcoma of the spleen, 1 soft tissue sarcoma, 1 ovarian sarcoma, 1 reticulum cell sarcoma, 1 spleen sarcoma, and 1 liver sarcoma.

Gibel et al. (1973) also studied the effects of dimethoate on mice. Percutaneous application of fresh solutions of dimethoate was given twice a week for six weeks on shaved back skin of AB mice of both sexes; the animals survived for only 270 days. Five animals out of 19 showed malignant tumors, of which there were four leukoses and one breast carcinoma. The spleen showed considerable metaplasia with often complete atrophy of white pulp. The follicles of the white pulp showed a loose narrow lymphocytic mantle around the central arteries. The trabecular framework of the spleen was generally narrowed and reduced. The red pulp showed a partially localized and diffuse myeloid proliferation with numerous immature cell forms which made it difficult to recognize the basic structure. The authors felt that mice also developed the myeloproliferative syndrome similar to that observed in rats.

The benign tumors observed in the control animals were exclusively fibroadenoma of the breast. The authors did not mention the incidence of malignant tumors in controls but implied that they did not find any malignant tumors in the control animals.

ii. The National Cancer Institute, 1977. In 1977 the National Cancer Institute (NCI) completed a feeding study with dimethoate (NCI, 1977). Osborne-Mendel rats of both sexes, 35 days old, were administered 250 and 125 parts per million (ppm) dimethoate in the diet. After 19 days the doses were reduced to half and the treatment was continued for an additional 61 weeks. The animals were observed for 115 weeks. The treatment groups consisted of 50 animals of each sex, and the matched controls consisted of 10 animals. Matched controls for aldrin, chlordane, dichlorvos, dieldrin, and heptachlor were used for evaluation because these studies were carried out concurrently with the dimethoate feeding study. Complete histopathology was carried out on all the animals. Statistical analysis of tumor incidence by site and type showed neither an excess incidence of any specific tumor type nor any increase in total tumors. The pathological evaluation of this study was done at Gulf South Research Institute. A summary of the survival data and number of tumor-bearing animals is shown in Table 2.

TABLE 2 - Dimethoate chronic feeding study - number and survival of tumor-bearing rats

Sex	Dosage Group	Effective Number[a]	Number TBA[b]	Percent	Percent surviving (weeks)		
					52	78	115[c]
Male	Pooled Control	58	36	62	92	87	47
Male	Matched Control	10	7	70	100	80	30
Male	Low	50	23	46	98	96	72
Male	High	49	24	49	92	82	58
Female	Pooled Control	60	43	72	97	95	73
Female	Matched Control	10	7	70	100	100	90
Female	Low	47	30	64	98	92	74
Female	High	45	21	47	88	67	51

[a] Total number of rats initially placed on test minus the number missing or autolyzed.

[b] Number of tumor-bearing rats.

[c] Denominator for survival percentages was the original number of animals minus those killed for diagnostic purposes. No animals were accidentally killed, and none were missing. Study terminated at 115 weeks.

NCI (1977) also studied the effects of dimethoate on B6C3F hybrid mice which were 35 days old. The compound was administered in the diet at 250 and 500 ppm dose levels, and the feeding was continued for 69 and 60 weeks, respectively. Animals were observed for an additional 24 and 34 weeks respectively, before sacrifice. All of the animals were necropsied and examined histopathologically. The data were statistically analyzed for each organ and tumor type. No dose-related increase in tumor incidence by site or total in either sex was found. The pathological evaluation of this study was carried out at Gulf South Research Institute. The data for total-tumor bearing animals are summarized in Table 3.

TABLE 3 - Dimethoate chronic feeding study - number and survival of tumor-bearing mice

Sex	Dosage Group	Effective Number[a]	Number TBA[b]	Percent	Percent surviving (weeks) 52	78	90[c]
Male	Pooled Control	96	31	32	94	92	85
Male	Matched Control	7	6	86	100	100	86
Male	Low	50	11	22	98	84	82
Male	High	50	11	22	96	96	92
Female	Pooled Control	80	14	18	96	90	83
Female	Matched Control	10	3	30	90	90	70
Female	Low	50	15	30	96	96	90
Female	High	49	12	24	94	94	90

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a/ Total number of mice initially placed on test minus the number missing or autolyzed.

b/ Number of tumor-bearing mice.

c/ Denominator for survival percentages was the original number of animals minus those killed for diagnostic purposes. No animals were accidentally killed, and none were missing. Study terminated at 90 weeks.

iii. Steiglitz et al., 1974. Steiglitz et al. (1974) studied the hematotoxic effects of dimethoate in rats. Dimethoate was administered to 10-week-old Wistar rats in doses of 5, 10, and 15 mg/kg body weight by oral intubation. Another group was given an intra-muscular dose of 15 mg/kg. Each test group consisted of 40 animals with two control groups of 40 animals each. The most important hematological results included pronounced hyperplasia of the hematopoietic parenchyma in the bone marrow, and sometimes strong, extraosseous myeloid metaplasia. Hyperplasia in the bone marrow occurred at different levels in all three hematopoietic cell systems with preferential involvement of granulocytopoiesis. Leukocytosis of varying intensity in the peripheral blood was also found but mainly affected granulocytes. The highest value exceeded 50,000/ul. The Agency did not base it RPAR on this third study because the study lacked sufficient detail. However, the Agency requested registrants and other interested parties to submit to the Agency information on these, or similar, effects of dimethoate.

b. The Agency's Conclusion in PD 2/3 Regarding the Requirement of an Additional Oncogenicity Study. In Position Document 2/3, the Agency concluded that the rebuttals did not invalidate the oncogenic risk criterion cited in the RPAR notice. However, based on re-analysis of the studies involved and the rebuttal comments as a whole, the Agency concluded in Position Document 2/3 that the weight of evidence for carcinogenicity of dimethoate is only suggestive, warranting further studies, but not adequate to justify a quantitative assessment of cancer risk.

c. Comments on Requiring an Additional Oncogenicity Study. The Scientific Advisory Panel (SAP), in its formal comments, disagreed with the Agency position to require an additional oncogenicity study. The SAP stated that the National Cancer Institute bioassay study (NCI, 1977) was a valid test for the oncogenic potential of dimethoate. Although the test was flawed, the SAP did not believe that the NCI study was flawed to the point where it is of no value in regulatory action. The SAP claimed that this position was also taken by the Agency's Carcinogen Assessment Group (CAG). For a discussion of flaws in the NCI (1977) study, see pages 64-66 of the Agency's Position Document 2/3 for Dimethoate and also pages 40 and 41 of the "Transcript of Proceedings" FIFRA Scientific Advisory Panel, Arlington, Virginia, November 29, 1979.

American Cyanamid [7(30000/16c)] argued that supportive evidence is lacking for determining that dimethoate is an oncogen. American Cyanamid further argued that conclusions made in the Gibel et al. (1973) study were based on inappropriately grouped data and that the National Cancer Institute study (NCI, 1977) is an adequate assessment of the oncogenic potential of dimethoate. American Cyanamid urged the Agency to accept the position taken by the Scientific Advisory Panel.

d. The Agency's PD 4 Response. The Agency's CAG (Albert, R.E., 1980) provided an additional response to the comments from SAP and American Cyanamid on the oncogenicity position in Position Document 2/3, wherein the Agency disagreed with the SAP position that further testing of dimethoate is not needed. The CAG indicated that if there were no other relevant considerations, then the negative NCI bioassay, flawed though it is, in conjunction with a lack of carcinogenicity of organic phosphate pesticides in general, might make further testing of dimethoate unnecessary. However, in the case of dimethoate there is substantial evidence for mutagenicity of dimethoate, coupled with suggestive evidence for carcinogenicity in the Gibel et al. (1973) study which was done on Wistar rats. The NCI bioassay (NCI, 1977) involved a different strain of rats, namely, the Osborne-Mendel rat. Furthermore, in these two studies there was clear evidence of hematopoietic toxicity in the Wistar rat but not in the Osborne-Mendel rat, thus indicating the possibility of a different metabolic handling of dimethoate or a difference in target-organ susceptibility in the two strains. In its response to the SAP recommendations the CAG emphasized (Albert, R.E., 1980), that it is not comfortable with the SAP position that no further oncogenicity testing of dimethoate be required.

Therefore, the Agency rejects the positions of SAP and American Cyanamid that there is sufficient evidence to determine that dimethoate is not an oncogen. Moreover, in order to more fully ascertain whether or not dimethoate poses a risk of oncogenicity, the Agency will require that a limited bioassay be conducted on the Wistar rat at the highest dose level used in the Gibel study (30 mg/kg by stomach gavage twice a week).

3. Teratogenic, Reproductive and Fetotoxic Effects Risk--a. Summary of Laboratory Animal Studies Cited in PD 1--i. Budreau and Singh, 1973. Budreau and Singh (1973) studied the effect of dimethoate on the reproduction of Charles River CD-1 mice. The insecticide was added to drinking water at the rate of 60 ppm (1/6 the LD_{50}) for five generations. Reproductive performance was evaluated by mating success and reproduction time. Mating success was calculated as the proportion of the females mated that had litters, expressed in percentages. Reproduction time was the number of elapsed days from the first day when the females were presented to the male to the day of delivery. The authors stated that dimethoate treatment significantly reduced mating success and increased reproduction time.

Second litter mating success ranged from 33 to 61% ($p<0.01$) and treated females required significantly longer periods than controls ($p<0.01$) to produce first litters in all generations. Survival rate of total pups and litters was significantly reduced ($p<0.01$) in generations I, III, IV, and V. Histologic examination of the mammary glands of treated females with high newborn mortality showed the glands were well developed and contained milk. The growth rate of dimethoate-treated pups usually fell behind that of controls, from day 12 after birth. On day 28, average weight was not always significantly different from controls, mainly because low-weight pups died.

ii. Scheufler, 1975. Scheufler (1975) administered a single 40 mg/kg dose of dimethoate, intraperitoneally, to female AB Jena/Halle mice on the day of conception. On the ninth day of pregnancy the author observed a significant increase in the number of dead embryos ($p<0.01$). When dimethoate was injected daily, at 40 mg/kg during the first 14 days of pregnancy, four times as many implanted embryos died in comparison to controls. When 40 mg/kg of dimethoate was administered to female C57BL mice, the number of nonpregnant females was increased to 70% as compared to 20 to 30% for controls. When dimethoate was applied to DBA-mice, 50% of the mated females showed no embryos. The author suggested that dimethoate appears to hinder strongly the development of embryos prior to implantation.

iii. The American Cyanamid Co., 1965. The American Cyanamid Co (1965(a)) conducted a three generation feeding study to determine whether dimethoate would interfere with reproduction or lactation. Albino mice of the CF1 strain were fed diets containing 5, 15, 50, and 0 (control) ppm of dimethoate. Animals were approximately one month old at the start of the test. Weaned pups were fed the same diets as their parents.

For mating purposes one male and two females were housed together. Females were housed alone while they cast and weaned their litters, after which parent animals were mated again. There were two mating periods. The report concluded that "reproduction and lactation performance was good for all groups".

b. Summary of Additional Laboratory Animal Study Cited in PD 2/3: Khera (undated). New data (Khera undated) showing a dimethoate formulation to be a mild teratogenic agent was received by the Agency after the RPAR was issued.

Khera (undated) administered Cygon 4E containing 47.3% dimethoate to pregnant cats (in gelatin capsules) on days 14 to 22 of gestation. The doses were 0, 3, 6, or 12 mg/kg per day of Cygon 4E which corresponds to 0, 1.4, 2.8, or 5.7 mg/kg per day of dimethoate. On day 43 of gestation, the fetuses were removed, weighed, and examined.

There were no signs of maternal toxicity in any cats treated. Dimethoate, at all doses tested, caused no effect on the number of live fetuses, resorption, dead fetuses, or mean fetal weight. Both the total number of anomalous fetuses and the number of litters having anomalous fetuses were increased at the high dose when compared to controls, but this increase was not statistically significant ($p=0.05$, Student's t Test). When the incidence of one abnormality (polydactyly, or increase in the number of digits on the paws) at the high dose was compared to the controls, the results were statistically significant.

There were no anomalies noted at 3 or 6 mg/kg and hence a no-observed effect level for all parameters can be set at 6 mg/kg per day of Cygon 4E. The author (Khera) indicated that the teratogenic effect observed in this study should be verified through additional testing. This additional testing would determine if the effect were due to dimethoate itself, the pesticidally inert ingredients, or the combination of these.

The same dimethoate formulation, Cygon 4E, was tested at doses of 0, 3, 6, 12, or 24 mg/kg per day (corresponding to 0, 1.4, 2.8, 5.7, or 11.3 mg/kg per day dimethoate) in pregnant Wistar rats by oral intubation. There were 20 female rats started in each group, and the number of pregnant dams was 17, 17, 15, 16, and 16 respectively. One dam at the highest dose died from Cygon-induced cholinergic signs of toxicity, and another seven showed similar signs of toxicity but recovered. Decreased maternal weight gain was seen at the high dose, but no adverse maternal effects were noted at the lower doses.

There were no effects of treatment on the number of live fetuses per dam, number of dead or resorbed fetuses, or fetal weight. At doses of 12 and 24 mg/kg per day Cygon 4E, there were significant increases in number of anomalous fetuses/number fetuses examined and the number of litters having at least one anomalous fetus/number of litters examined, when compared to controls.

When individual variations were examined, the two high doses had a significant ($p=0.05$) increase in fetuses with wavy ribs. The author (Khera) characterized these anomalies as being "of minor types and of unknown significance". It should be noted that these effects (wavy ribs), which are often considered indicators that the the embryotoxic or fetotoxic dose is approached, occurred at either the maternal toxic dose or one-half of that dose.

In both studies by Khera, the no-observed effect level was 6 mg/kg per day for Cygon 4E (2.8 mg/kg per day dimethoate). The occurrance of minor teratogenic effects at higher doses indicates that Cygon 4E has the potential to interfere with fetal development. Additional studies are required to fully determine the significance of these findings.

c. The Agency's Conclusion in PD 2/3 Regarding General Reproduction and Fetotoxic Effects and Teratogenic Effects. In Position Document 2/3, the Agency reviewed the rebuttals and additional information submitted (Courtney, K. D., 1978; and Khera, undated). Based on that evaluation, the Agency concluded that the rebuttals did not invalidate the Agency's original presumption of risk on general reproductive effects or on fetotoxic effects based on the three studies (Budreau and Singh, 1973; Scheufler, 1975(a); and American Cyanamid Co., 1965a) cited in the RPAR notice. In addition, the new study (Khera, undated) showed Cygon 4E, a dimethoate formulation containing 47.3% dimethoate, to be a mild teratogenic agent.

d. Comments on No Observed Effect Level (NOEL). American Cyanamid [7(30000/16c)] commented that the Budreau and Singh (1973) study established an effect level and that for a study to be useful in a risk assessment process a no observable effect level (NOEL) must be established. American Cyanamid then recommended that the NOEL of 50 ppm in the diet obtained in their own study (American Cyanamid, 1965a) be used for risk assessment.

e. The Agency's PD 4 Response. The Agency agrees that the Budreau and Singh (1973) study is unacceptable for risk assessment, but rejects the recommendation that the NOEL of 50 ppm obtained in the American Cyanamid Study (1965a) be used for risk assessment of dimethoate. Budreau and Singh (1973) observed effects on reproduction at 60 ppm, the only dose level tested. A no observed effect level was not be established. American Cyanamid (1965a) observed no effects in their reproduction study in which three dose levels (5 ppm, 15 ppm, and 50 ppm) were used. Although this study used more than one dose level, none of the doses produced a significant reproductive effect and thus a no observed effect level could not be established.

In the absence of a no-effect level for reproductive effects per se, the Agency will use the NOEL of 2.8 mg/kg per day from the Khera study for the risk assessment of all reproductive effects, including fetotoxic and teratogenic effects, as well as fertility related reproductive effects.

The Agency believes this approach is justifiable because its concern extends to all adverse reproductive effects (including teratogenicity, fetotoxic, and reproductive effects such as reduced fertility) that may result from exposure to dimethoate. Since the effects in Khera's (undated) teratogenicity study were observed at lower levels than effects in the reproductive studies, the use of the no-effect level from the teratogenicity study will provide ample protection for reproductive as well as teratogenic fetotoxic effects.

f. Comments on the Need for Additional Reproductive Studies. The SAP, in its formal comments, indicated that additional reproductive studies are necessary to assess the effect of dimethoate on male reproduction. The Panel noted positive effects in two studies on reproduction, implying the possibility of effects on males.

g. The Agency's PD 4 Response. The Agency believes that American Cyanamid's multi-generation reproduction study which showed no adverse effects in males is sufficient to establish that dimethoate does not have a significant potential to adversely effect male reproduction. However, the Agency will require additional teratology studies on the technical dimethoate in 2 species of laboratory animals as specified in the proposed guidelines (FR 43, No. 163, Tuesday, August 22, 1978).

h. Comments on the Khera (undated) Study. American Cyanamid [7(30000/16c)] indicated that:

(1) No dose-response effect was noted in either the cat or rat teratology study by Khera.

(2) The only response noted was in the high dose group and consisted of an increase in a common anomaly; i.e., wavy ribs in rats and polydactyly in cats.

(3) Dr. Khera, himself, concluded "from the data available, it cannot be definitely ascertained whether treatment with 12 mg Cygon 4E per kg has in any way contributed to the expression of polydactyly."

i. The Agency's PD 4 Response. In response to the first point, the Agency noted that, in the rat study, there was a definite dose-response relationship in terms of a statistically significant increase in the number of litters with anomalous fetuses. Looking at each particular anomaly, there was a signficant increase in the number of fetuses having wavy ribs and a non-significant increase in fetuses having extra ribs at a dose level of 12 mg/kg Cygon 4E.

In response to American Cyanamid's second point, the Agency has concluded that its concern is not alleviated because the adverse effect noted was merely an increase in the background rate of normally occurring anomalies. The occurrence of minor teratogenic effects at higher doses indicates that Cygon 4E has the potential to interfere with fetal development. The increase in minor anomalies indicates that dimethaote may pose a potential to produce adverse fetotoxic or teratogenic effects in humans.

On the third point, the Agency notes that, in the Khera study, a statistically significant increse in anomalies occurred at 12 mg/kg Cygon 4E when compared to the controls. Although the data from the Khera study is limited and does not assess the potential for dimethoate to produce fetotoxic/teratogenic effects at a range of dose levels, this data does suggest that dimethoate may have the potential to interfere with normal fetal development.

j. Comments on Wavy Ribs. The SAP, in its formal comments, commented on the teratogenic studies and was unable to confirm that wavy ribs are a true teratogenic effect.

k. The Agency's PD 4 Response. The Agency has concluded that the difference between a "true" teratogenic effect and an increase in minor anomalies which occur at a normal background rate should not be relevant for regulatory purposes. The increased incidence of minor teratogenic effects indicates that dimethoate may have the potential to interfere with fetal development. Hence, the Agency's concern about possible adverse effects to the population at risk is not diminished. Until such time as the Agency is able to establish that the adverse effects noted in the Khera study do not indicate a potential risk for humans, the Agency will treat these effects as warranting regulatory concern.

4. Mutagenicity Riks--a. Summary of Studies Cited in PD 1 on Dimethoate-Induced Mutations in Submammalian Test Systems--i. Fahrig, 1973. Fahrig (1973) treated cultures of Saccharomyces cerevisiae with dimethoate at seven dosage levels (ranging from 40 mM to 100 mM). The author(s) did not indicate whether a metabolic activation system had been included in the test procedures. An induction of mitotic gene conversions, demonstrating a positive mutagenic effect was observed.

ii. Hanna and Dyer, 1975. Hanna and Dyer (1975) tested dimethoate in two bacterial systems by adding 5 to 10 ul of dimethoate to a layer of the bacterial strain. Positive results were observed in two strains of *Escherichia coli* (*E*., *coli* WP2 uvrA and *E*. *coli* WP 67). Negative results were seen in several *E*. *coli* and *Salmonella typhimurium* strains.

iii. Mohn, 1973. Mohn (1973) studied the effect of dimethoate in *E*. *coli* K-12/galRs18. Dimethoate was shown to have mutagenic activity. A significant dose-response relationship was obtained using five dosage levels (from 1 to 6 X 10^{-3}M). The author(s) did not indicate whether a metabolic activation system had been included in the test procedures.

iv. American Cyanamid Co., 1977. American Cyanamid Co. (1977) investigated the mutagenic potential of dimethoate using several strains of *S*. *typhimurium* and one strain of *E*. *coli*. Rat liver microsomal enzymes (S-9) were used for metabolic activation. No mutagenic effects were observed. Doses ranged from 20 to 100 ug/plate.

v. Shirasu et al., 1976. Shirasu et al. (1976) studied the mutagenic effect of dimethoate in the H17 Rec^+ and $R45^-$ strains of *Bacillus subtilis*. No mutagenic activity was observed under the conditions of the study. The dose of dimethoate used was not given.

vi. Agarwal et al., 1973. Agarwal et al. (1973) studied the effect of dimethoate on seed setting and germination in the bean (Phaseolus vulgaris). Dimethoate in concentrations of 0.1 and 0.5% by volume were used as foliar sprays on bean plants in four observation plots. The spraying was done at the time of bud initiation. Seeds were then collected and soaked up to 48 hours at room temperature. Dimethoate reduced germination 23 to 28% below controls. Chromosomal abnormalities including fragments, stickness, and anaphase bridge formation were seen in 12.8 to 27.5% of the treated series. No abnormalities were seen in the controls.

vii. Amer and Farah, 1974. Amer and Farah (1974) studied the cytological effects of dimethoate on cotton (Gossypium barbadense) and beans (Vicia faba). Bean seeds were treated at concentrations of 0.5, 0.25, 0.125, and 0.0625% using both pure and formulated (solution containing 40% active ingredient) dimethoate. Cotton seeds were treated with the formulated product at concentrations of 0.25, 0.125, and 0.0625% dimethoate. Both pure and formulated dimethoate greatly inhibited cell division in beans. The mitotic index for bean seeds treated with pure dimethoate ranged from 18.4 (0.5% dimethoate) to 62.6 (0.625% dimethoate) compared with a mitotic index of 94.1 for controls. The mitotic index for beans treated with formulated dimethoate ranged from 8.0 (0.25% dimethoate) to 42.0 (0.0625% dimethoate) compared with 56.4 for controls. Chromosomal abnormalities were also observed for all treated seeds. The percentage of abnormal mitoses in beans induced by formulated dimethoate was much higher than that induced by pure dimethoate.

b. Summary of Studies Cited in PD 1 on Dimethoate-Induced Mutations in Mammalian Test Systems--i. Gerstengarbe, 1975. Gerstengarbe (1975) investigated the ability of dimethoate to induce dominant-lethal mutations in the mouse (*Mus musculus*). Dimethoate was administered intraperitoneally to male mice of an inbred, AB Jena/Halle strain. One set of mice received a one-time dose of 80 mg/kg, while another group received 6.66 mg/kg daily for 30 days. The treated males were then paired with untreated females. The number of implantations, resorptions, and living and dead fetuses on the eighteenth day of gestation was determined. The living fetuses were weighed and separated according to sex. A signficant increase in the resorption rate was detected, indicating damage during spermiogenesis. A significant increase was observed in the mutation index indicating that dimethoate, in the case of AB Jena/Halle mice, induces dominant-lethal mutations and is capable of reaching germinal tissue.

ii. Bhunya and Behera, 1975. Bhunya and Behera (1975) injected adults of both sexes of the mouse (*Mus musculus*) with 1 cc/100 g body weight of dimethoate (0.5 and 1.0% solutions). Control animals were injected with distilled water. Standard cytological slides were prepared from bone marrow cells of animals sacrificed at 24, 48, and 72 hours after treatment. The authors stated that in the treated animals, in addition to other aberrations, centromeric fission and stretching were predominant. The number of chromosomes with breakage at the centromere ranged from 1 to 38 per cell. The frequency of aberrations was highest at 24 hours, moderate at 48 hours, and least after 72 hours for both doses tested. Aberration rates in control animals were not reported.

c. The Agency's Conclusion in PD 2/3 Regarding Additional Mutagencity Studies. After reviewing the comments and rebuttals on the mutagenicity risk presumption, the Agency concluded in PD 2/3 that the risk had not been rebutted. Section II c(2) of Position Document 2/3 presented an analysis of the mutagenicity studies on dimethoate and attempted to draw conclusions relative to human risk from dimethoate's ability to induce mutagenic effects. The Agency concluded that since insufficient data exist upon which to base a mutagenicity risk assessment, additional studies are required to estimate the magnitude of the risk.

d. Comment Contending that Dimethoate is not Mutagenic in the Ames System. In response to the Agency's RPAR Notice (PD 1) for dimethoate, American Cyanamid Co. submitted a bacterial assay as their rebuttal (Rebuttal Comment 30000/16:#5A). American Cyanamid Co. used E. coli WP-2 $uvrA^-$ in their assay and found that "Dimethoate was not mutagenic" even at "extremely high doses". Based on their study, American Cyanmid Co. stated that dimethoate is a non-mutagen because of its "potency" of less than 0.01 revertants/nanomole.

In its Preliminary Notice of Determination Concluding the RPAR for Dimethoate (PD 2/3), the Agency rejected the American Cyanamid Co. rebuttal attempt. In their comments [7(30000/16c)] in response to PD 2/3, American Cyanamid Co. reaffirmed their contention that dimethoate is not mutagenic in the Ames System and that, based on McCann et al., 1975, Cyanamid made a determination that chemicals having mutagenic potencies of less than 0.01 revertants/nanomole can be classified as non-mutagens in the bacterial reverse mutation assay.

e. The Agency's PD 4 Response. American Cyanamid's statement that dimethoate is a non-mutagen is not correct by the criterion that it has a "potency" of less than 0.01 revertants/nanomole. The registrant was attempting to use a cut-off point derived from an Ames test with a Salmonella organism (McCann et al., 1975) to describe the potency for an E. coli test system in which a clear dose-response was observed. Clearly, the level of revertants viewed as indicating a positive response in one test species has little relevance to the potency determination in a different test system. The usually accepted criteria for a positive in an Ames test is a doubling of the background rate and a dose-response effect. The important aspect of the E. coli test in question here is the dose-response observed. The potency level from the Salmonella sp. study is irrelevant.

Furthermore, this particular method of defining a cut-off point, cited by American Cyanamid, was arbitrarily chosen by McCann et al. (1975) in order to relate mutagenicity to carcinogenicity and it appears only in the McCann et al. (1975) paper. Other more recent methods of defining a positive mutagenic response do no include any cutoff point (DeSerres et al., 1979). DeSerres et al. (1979) is currently considered to be the most valid protocol recommendation for using the Salmonella/Microsome Mutagenicity Assay.

f. Comments on the Agency's Requirement of a Dominant Lethal Test. American Cyanamid [7(30000/16c)] in their comments on PD 2/3 stated that they have no comment on the requirement for a dominant lethal test except to point out that a recently published negative report using this procedure to evaluate dimethoate in the mouse is available as an abstract (Degraeve et al., 1979).

g. The Agency's PD 4 Response. The Agency has been unable to obtain a copy of the Degraeve study and, therefore, can not evaluate this study solely on the basis of an abstract. The Agency will welcome any additional information on the Degraeve et al. (1979) study, or any other dominant lethal test using dimethoate, and will evaluate such information upon its receipt.

5. Delayed Neurotoxicity--a. Summary of Laboratory Animal Studies Cited in PD 1: American Cyanamid Co., 1965. American Cyanamid Co. (1965b) performed demyelination studies for dimethoate and its oxygen analog, dimethoxon, in white leghorn hens estimated to be 1 to 2 years of age. Although the results appear to show that these chemicals did not cause myelin degeneration, a closer examination of these reports indicates that the tests were inconclusive for the following reasons:

(1) An LD_{50} for 24 hours, instead of 7 days, should have been used in the tests.

(2) Since hens were given the chemicals in their feed, the dose received by each hen was not accurately known. Administration of the test substance should have been by intubation or gelatin capsule.

(3) Since maximum doses of only one-eighth LD_{50} were administered, delayed neurotixic effects may not have developed.

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The regimen of the study was such that the study would not detect delayed neurotoxicity for some compounds that have a known potential to cause this effect. Either much higher doses, i.e., the maximally tolerated dose using atropine, or sub-acute studies for longer periods of time should have been used.

The Agency did not presume against dimethoate on the basis of this study, but instead requested registrants or other interested parties possessing information relevant to dimethoate associated delayed neurotoxicity effects to submit such data to the Agency.

b. The Agency's Conclusion in PD 2/3 Regarding Delayed Neurotoxicity Testing. The Agency concluded in Position Document 2/3, after reviewing comments submitted in response to PD 1, that insufficient evidence exists to determine whether dimethoate can induce delayed neurotoxicity and that the submission of new evidence concerning dimethoate's ability to induce delayed neurotoxic effects is warranted.

c. Comments on the Agency's Requirement for Another Delayed Neurotoxicity Study. The SAP, in its formal comments, requested the Agency to reevaluate the need for additional delayed neurotoxicity studies in view of research reported by T.B. Gaines (1969) entitled "Acute Toxicity of Pesticides" in which no paralysis was observed in tests conducted with dimethoate.

d. The Agency's PD 4 Response. In response to the SAP comment concerning the requirement for additional delayed neurotoxicity studies, the Agency has reevaluated the American Cyanamid delayed neurotoxicity studies (1965b) and has reviewed the T.B. Gaines study (1969) entitled "Acute Toxicity of Pesticides".

In the American Cyanamid Studies (1965b), the chemical was administered in feed and the dosage received by each hen was not accurately known. Since maximum doses of only one-eighth the LD_{50} were administered, delayed neurotoxicity effects may not have developed. These studies were inconclusive with regard to dimethoate's delayed neurotoxic potential.

The T.B. Gaines (1969) study entitled "Acute Toxicity of Pesticides" is primarily a report on the determination of LD_{50} values for 98 pesticides and 2 metabolites of DDT using adult Sherman strain rats treated with a single dose of the test substance by the oral or dermal route. The author only briefly reports on the screening tests for paralytic effects in chicken hens treated with carbamate and organic phosphorus pesticides.

The author stated that "The method for conducting the screening tests for the paralytic effects of carbamate and organic phorphorus pesticides in chickens was the same as that described by Durham et al. (1956), with the exception that many of the compounds reported in that paper were tested in White Leghorn chickens because of the unavailability of the Rhode Island Red breed". The Gaines study indicates that each test chicken was administered atropine sulfate in water solution orally at a dosage level of 15 mg/kg to protect them against the acute effects of the test substances. 9 carbamate and 30 organic phorphorus compounds, including dimethoate, were tested for paralytic effects. Fifteen minutes after administration of the atropine sulfate the chickens were administered the test substance in peanut oil solution or in suspension by subcutaneous injection under the right wing. The chickens were checked daily for signs of paralyis by placing them on the ground and observing their ability to walk. The author reported that no paralysis was observed in chickens dosed with dimethoate.

Several important details, such as the number of animals used, the dosage level for the test substance, and whether or not histopathology on nervous tissue was carried out, were not given in the study.

After reevaluating both the American Cyanamid studies (1965b) and the Gaines (1969) study the Agency concludes that not enough data are available in these studies to make a hazard determination. Therefore, the Agency will require additional delayed neurotoxicity studies in order to allow the Agency to make a hazard determination for delayed neurotoxic effects due to exposure to dimethoate.

6. Exposure Analysis - Dietary Exposure--a. The Agency's Exposure Calculation in PD 2/3. The Agency, in calculating a worst case estimate of the dietary exposure of the general population to dimethoate in Position Document 2/3, assumed dimethoate residues to be present on food at the tolerance levels. However, not all crops for which dimethoate is registered are actually treated with dimethoate. Therefore, in its calculation of a probable case estimate of oral exposure, the Agency factored in the percentage of crops actually treated with dimethoate.

b. Comment on the Agency's Calculation of Dietary Exposure. The SAP, in its formal comments, agreed, in general, with the approach used by the Agency in calculating dietary exposure, but added that in view of the biodegradability of dimethoate it is unlikely that the dietary level for this compound would approach tolerance levels.

c. The Agency's PD 4 Response. The Agency agrees with the SAP. In Position Document 2/3 the Agency stated that "it is generally recognized that organophosphate pesticides, such as dimethoate, degrade rather rapidly and that several weeks may elapse between application and consumption of the treated crop. Therefore, it is likely that the Margin of Safety (MOS) for general population risk is several orders of magnitude higher than the 875 calculated as a probable case. However, a lack of data concerning dimethoate residues at harvest precludes estimates of the actual MOS". Risk from dietary exposure was not viewed by the Agency as a problem in PD 2/3. A calculation of the dietary exposure resulting from a single serving of selected food items confirms that dietary exposure is not a problem. The SAP has confirmed the Agency's belief that risk from dietary exposure is not an issue of concern. See Table 4 below for a comparison of the MOS (including dietary exposure) and the MOS (excluding dietary exposure) for various users of dimethoate.)

TABLE 4 - Margins of safety for various users of dimethoate

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE	ORAL EXPOSURE	TOTAL EXPOSURE	MOS (INCLUDING ORAL EXPOSURE)[1]	MOS (EXCLUDING) ORAL EXPOSURE)[1]
Citrus	Ground (air blast)	Applicators[2] Mixers/loaders	0.39	0.0032	0.03932	7	7
Veg. Fields	Air	Pilots	0.013	0.0032	0.0162	170	215
Veg. Fields	Air	Flaggers	0.013	0.0032	0.0162	170	215
Veg. Fields	Air	Mixers/ loaders	0.0062	0.0032	0.0094	298	452
Pecans	Ground (air blast)	Applicators[2] Mixers/loaders	0.119	0.0032	0.122	23	24
Pome	Ground (air blast)	Commercial Applicators, Inc. Mixers/loaders	0.242	0.0032	0.245	12	12
Pome	Ground	Hose Sprayers	0.00017	0.0032	0.0034	823	16,471
Corn	Air	Pilots	0.0083	0.0032	0.012	233	337
Corn	Air	Flaggers	0.008	0.0032	0.011	255	350
Corn	Air	Mixers/Loaders	0.0063	0.0032	0.010	280	444
Grape	Ground	Boom highest conc.	0.0012	0.0032	0.0044	636	2,333
Grape	Ground	Highest conc. (custom) Copplestone model	0.0207	0.0032	0.0239	117	135
Grape	Ground	Dust	0.130	0.0032	0.1332	21[3]	22[3]

[1] Based on a 2.8 mg/kg NOEL (Khera undated).

[2] Applicator is also mixer/loader.

[3] Exposure via inhalation.

7. Exposure Analysis - Occupational Exposure--a. The Agency's Occupational Exposure Calculations in PD 2/3. In Position Document 2/3 the Agency revised and expanded the exposure analysis presented in Position Document 1. The exposure analysis in PD 2/3 was developed for smaller subpopulations engaged in the application of dimethoate, who would experience greater exposure than that identified for the general population. For example, before application, mixers and loaders may be exposed both dermally and via inhalation as the result of splashing, vaporization, or accidental spills; during application, pilots and flaggers involved in aerial application, as well as ground application, may be exposed both dermally and via inhalation. Estimates of exposure to these subpopulations and the MOS for each are presented in Table 5.

TABLE 5 - Estimates of exposure and margins of safety for various users of dimethoate[1/]

CROP	TYPE OF SPRAYING	MOS FOR SUBGROUP	Combined Dermal and Inhalation DAILY EXPOSURE (for female mg/kg/day)	ORAL EXPOSURE	TOTAL EXPOSURE	MOS For Teratogenic Effects[2/]
corn	air	pilots	0.0083	0.0032	0.012	233
corn	air	flaggers	0.008	0.0032	0.011	255
corn	air	mixers/loaders	0.0063	0.0032	0.010	280
ornamental	ground	commercial high concentration compressed air	0.00012	0.0032	0.0033	843
ornamental	ground	home garden high concentration	0.000152	0.0032	0.00335	836
grape	ground	Boom highest conc.	0.0012	0.0032	0.0044	636
grape	ground	highest conc. (custom) Copplestone model	0.0207	0.0032	0.0239	117
grape	ground	dust	0.130	0.0032	0.1332	21
cotton	air	pilots	0.0017	0.0032	0.005	560
cotton	air	mixers/loaders	0.00095	0.0032	0.0042	667
cotton	ground	applicators	0.0078	0.0032	0.0011	255
cotton	ground	mixers/loaders	0.00033	0.0032	0.004	700
citrus	air	pilots, ground crews, mixers/loaders	same as corn			

[1/] From PD 2/3.

[2/] Based on 2.8 NOEL (Khera undated).

TABLE 5 - Estimates of exposure and margins of safety for various users of dimethoate[1]

CROP	TYPE OF SPRAYING	MOS FOR SUBGROUP	Combined Dermal and Inhalation DAILY EXPOSURE (for female mg/kg/day)	ORAL EXPOSURE	TOTAL EXPOSURE	MOS For Teratogenic Effects[2]
citru.	ground (air blast)	applicators mixers/loaders	0.39	0.0032	0.3932	7
sorghum	air	same as corn				
veg. fields (tomato, broccoli)	air	pilots flaggers mixers/loaders	0.013 0.013 0.0062	0.0032 0.0032 0.0032	0.0162 0.0162 0.0094	170 170 298
veg. (Fla)	ground	applicators	0.00005	0.0032	0.0033	848
vector control (house fly)	ground	applicators	0.0019	0.0032	0.0051	549
forest pine (seed orchard)	ground	applicators	0.0008	0.0032	0.0040	700
pecan high conc.	ground	applicators mixers/loaders	0.00044 0.00022	0.0032 0.0032	0.0036 0.00342	778 819
pecan	ground (air blast) model	applicators mixers/loaders	0.119	0.0032	0.122	23
safflower	air	same as corn				
pome	ground (air blast)	commercial applicators including mixers/loaders	0.242	0.0032	0.245	12
pome	ground	hose sprayers	0.00017	0.0032	0.0034	

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[1] From PD 2/3.

[2] Based on 2.8 NOEL (Khera undated).

The exposure analyses in PD 2/3 considered rebuttal comments received in reponse to the RPAR notice, data from the USDA concerning use and use practices, published studies concerning worker exposure to dimethoate and related pesticides, and certain assumptions made by the Agency in the absence of specific data on dimethoate.

There were no published data available to the Agency showing the amount of dimethoate an applicator would be exposed to during aerial application. However, exposure data were available for another organophosphate, parathion. Therefore, the Agency used exposure values reported for parathion aerial application (Gordon et al., 1978) as a model for estimating human exposure to dimethoate during aerial application. The following rationale was given for using parathion values to estimate dimethoate exposure:

(1) The vapor pressure of parathion and dimethoate are comparable. It is generally recognized that the residues of pesticides with relatively low volatility in the air during or immediately after application are predominantly present in the form of droplets and particles.

(2) The formulation most often used for both parathion and dimethoate is an emulsifiable concentrate (E.C.).

(3) The rates of aerial application of parathion and of dimethoate are similar.

Since exposure during aerial application can occur via the respiratory and/or dermal route, the Agency made calculations of applicator exposure via each of these routes.

In calculating inhalation exposure, the Agency made the following assumptions:

(1) The ambient air concentrations observed for parathion (Gordon et al., 1978) are the same as dimethoate at each of the various sampling sites (e.g., airplane cockpits).

(2) The applicator's breathing rate will be 1.8 m^3 per hour.

(3) 100% of all dimethoate inhaled will be absorbed.

(4) The applicator will weigh 60 kg (adult female).

(5) The applicator will wear no special protective devices (e.g., respirator).

The Agency used the following equation in calculating the respiratory exposure for dimethoate:

$$\text{Respiratory Exposure (ug/kg/day)} = \frac{\text{Ambient air concentration of dimethoate (ug/m}^3\text{) at the site in question} \;X\; 1.8\ \text{m}^3/\text{hr (breathing rate)} \;X\; \text{Number of hours of exposure/day}}{\text{60 kg person}}$$

For the dermal exposure calculations the Agency made the following assumptions:

(1) Dermal exposure observed for parathion skin patch tests (Gordon et al., 1978) are the same for dimethoate.

(2) 15% of the applicator's total skin surface will be exposed.

(3) 10% of the dimethoate coming into contact with the uncovered skin will be absorbed.

(4) The applicator will weigh 60 kg (adult female).

The following equation was used by the Agency in calculating the dermal exposure to dimethoate:

$$\text{Dermal Exposure (mg/kg/day)} = \frac{\text{Concentration of dimethoate on the skin (ug/cm}^2\text{)} \times 3000\ \text{cm}^2 \times 10\%\ \text{absorbed} \times \text{Number of hours exposed per day}}{60\ \text{kg person}}$$

Specific data concerning applicator exposure to dimethoate applied by boom type equipment in large agricultural situations and by compressed air equipment (hand pump sprayers) in home garden application situations in the United States was not available to the Agency. However, information concerning applicator exposure to dimethoate in the Sudan was available (Copplestone et al., 1976). Therefore, in PD 2/3 the Agency used the dermal and respiratory exposure of spraymen to dimethoate reported by Copplestone et al. (1976) as the basis for its calculations of applicator exposure to dimethoate when boom and compressed air equipment is used.

The Agency used the following equations to calculate the respiratory and dermal exposure resulting from the ground application of dimethoate:

$$\text{Respiratory Exposure} = \frac{\text{Respiratory exposure observed in Sudan (mg/hr)} \times \dfrac{\text{concentratin of dimethoate used in the U.S.}}{\text{concentration of dimethoate used in the Sudan}} \times \text{Number of hours spraying (USDA/states/EPA Assessment Team on Dimethoate)}}{\text{60 kg person}}$$

$$\text{Dermal Exposure} = \frac{\text{dermal exposure observed in the Sudan (mg/cm/hr}^{2}\text{)} \times \dfrac{\text{concentration of dimethoate used in the U.S.}}{\text{concentration of dimethoate used in the Sudan}} \times \text{10\% absorption}}{\text{60 kg person}}$$

Specific data concerning applicator exposure to dimethoate applied by high volume air blast equipment (greater than 300 gal./A), such as that commonly used in citrus, pecans, and pome fruit orchards, were not available to the Agency. However, Wolfe et al. (1967) reported the dermal and respiratory exposure of workers to several selected pesticides, one of which was parathion, using air blast equipment. In the absence of specific dimethoate data, the Agency, in Position Document 2/3, assumed the exposure values of workers applying 0.05% parathion emulsifiable concentration (E.C.) with air blast equipment to be the same as that for workers applying dimethoate. The Agency felt this assumption to be reasonable since both dimethoate and parathion are organophosphates and both are emulsifiable concentrates applied at similar concentrations.

The Agency concluded, in Position Document 2/3, that potential occupational exposure was greatest for ground applications of dust formulations on grapes and for ground applications utilizing air blast equipment on citrus, pome fruits, and pecans.

b. Comments on the Inadequacy of the Data Used to Estimate the Potential Exposure of Air Blast Applicators. A number of commenters concluded that the data on which the Agency relied in estimating the potential exposure of air blast applicators were inadequate. American Cyanamid [7(30000/16c)] and the University of California [8(30000/16c)] stated that the Copplestone (1976) study referred to in Position Document 2/3 was an inappropriate model for air blast exposure, since in that study dimethoate was applied with a knapsack mist blower. The University of Arizona [5(30000/16c)] commented that they are concerned about the small amount of data on which the Agency relied, i.e. "an old study in Washington State by Dr. Homer Wolfe, and an incident in Sudan" (Wolfe, 1967 and Copplestone, 1976).

c. The Agency's PD 4 Response. The Agency responds to these comments regarding the inadequacy of the data relied upon in PD 2/3 for estimating potential exposure of air blast applicators by pointing out, first of all, that the data used in the air blast calculations were that of Wolfe et al. (1967) and not that of Copplestone et al. (1976). Wolfe et al. reported dermal and respiratory exposure of workers to several selected pesticides, one of which was parathion, using air blast equipment. Secondly, the Agency did not have specific data on dimethoate exposure from air blast application for calculating exposure in PD 2/3. Therefore, in the absence of better information, the Agency extrapolated Wolfe's results with parathion to dimethoate. It is the Agency's opinion that the data were adequate for such an extrapolation and that such an extrapolation was reasonable since both dimethoate and parathion are organophosphates and both are emulsifiable concentrates applied at similar concentrations.

d. Comments on a University of California at Riverside Field Monitoring Study of Applicator Exposure to Organophosphate Pesticides Resulting from Use of Oscillating Boom Sprayers and Air Blast Equipment. The University of Arizona [5(30000/16c)], in their comments on PD 2/3, stated that a study on air blast sprayer driver exposure is underway at Riverside, California. This commentor recommended that a decision on air blast application be delayed until data from this study are available for scientific review. Additionally, the University of Arizona stated that it was their understanding that the study would be completed by August 1980.

The Scientific Advisory Panel, in its formal comments, mentioned testimony by a representative from the State of California relative to planned research in the near future, with dimethoate, to assess applicator exposure from air blast equipment in comparison with oscillating boom type sprayers.

The University of California at Davis [8)30000/16c)] stated, in their comments on PD 2/3, that "the Western Region Pesticide Impact Assessment Program is funding a study by Professors Gunther and Carman (University of California, Riverside) to quantify the extent of occupational exposure of pesticide applicators during actual spraying of an organic phosphate insecticide on citrus trees. Those studies will involve measurements of pesticide vapors and aerosols in the cab of the spray rig as a result of having the windows opened, opened and closed on operator judgment basis, and closed with and without air-conditioning. This will determine whether operator judgment is sufficient to limit pesticide exposure or whether a static cab or a more sophisticated system involving charcoal filters and air-conditioning units should be required. The principal investigators are willing to expand the experimental design to permit exposure comparisons between air blast and oscillating boom applications, providing adequate funding is available".

The California Citrus Quality Council [9(30000/16c)] stated that "The citrus industry of California is supportive of exposure studies now being undertaken at The Citrus Research Center of the University of California in Riverside to quantify applicator exposures associated with oscillating boom equipment and would fully endorse an extension of these studies to include evaluations with air blast equipped with various provisions for applicator protection and operated under variant field conditions".

e. The Agency's PD4 Response. The Agency agrees that actual data on applicator exposure to dimethoate would be more useful than estimates derived from an evaluation of other organophosphate pesticides. The Agency understands that the monitoring phase and the analysis of the data of the current study at the University of California are likely to be completed in early 1981. The Agency welcomes any additional information resulting from the current study at the University of California at Riverside.

8. Risk of Alternatives to Dimethoate--a. Summary of the Agency's Toxicology Review of Alternatives to Dimethoate. The Agency's purpose for reviewing alternatives for a particular pesticide is not to make an in-depth review of an alternative but to indicate whether or not suitable alternatives exist at each use site for the pesticide in question. In its toxicology review of the alternatives to dimethoate

the Agency reviewed available toxicity data from published and unpublished Substitute Chemical Program reports, proprietary data from pesticide petitions, and published literature. The basic conclusion of the Agency's review was that for the sites in which dimethoate is used, there are many alternatives.

In PD 2/3 the Agency proposed the cancellation of air blast application of dimethoate on citrus, pome fruit, and pecans. When cancellation of a use is considered by the Agency, a review of possible alternatives for the uses in question is conducted. A summary of the Agency's toxicological review of the alternatives for air blast application of dimethoate in citrus, pome fruit, and pecans is given below.

i. Alternatives to Dimethoate Use on Citrus. The Agency considered malathion, phosphamidon, formetanate, rotenone, demeton, mevinphos and parathion as the major alternatives to dimethoate use on citrus.

1. Malathion. Malathion is low in toxicity and has not been shown to cause adverse reproductive effects when tested in a teratology test. Recent National Cancer Institute studies have indicated no significant carcinogenic potential from malathion. Malathion was registered many years ago, but adequate multi-generation studies have not been performed.

2. Phosphamidon. Phosphamidon is more acutely toxic than dimethoate. A recent National Cancer Institute study

indicated that phosphamidon was not carcinogenic in B6C3F1 mice but the data were insufficient to allow interpretation in the rat. Data on reproductive effects are either lacking or carried out at Industrial Bio-Test. Validation of the Industrial Bio-Test studies has not been done. Phosphamidon, like malathion, was registered a number of years ago.

3. Formetanate. Formetanate is a much more acutely toxic compound than dimethoate with an oral LD_{50} around 20 mg/kg. Although available data indicate no significant adverse effects, the presence of Industrial Bio-Test data limits the usefulness of these studies.

4. Rotenone. Minimal data are available on rotenone's reproductive effects. Preliminary data suggested that rotenone was carcinogenic but evaluation of all of the carcinogenicity data does not indicate an oncogenicity hazard. Although there are some studies that indicate potential teratogenic problems, these studies are seriously flawed and need to be re-done before we can determine if there is a teratogenicity problem.

5. Demeton. Demeton is a highly toxic organophosphate (acute oral LC_{50} below 20 mg/kg). There appears to be no multi-generation study and the only teratogenic study seems inadequate to assess teratogenic or fetotoxic hazard. No chronic or carcinogenic studies have been reported.

6. Mevinphos. Mevinphos, like demeton, is a highly toxic organophosphate. Available teratogenic, reproduction, and chronic studies indicate no adverse effects.

7. Parathion. Parathion is a highly toxic organophosphate by all routes of exposure. A recent oncogenic study by NCI indicated positive findings. A preliminary risk assessment on the oncogenic effects is being carried out.

ii. Alternatives to Dimethoate Use on Pome Fruit (apples). The Agency considered cyhexatin (plictran), guthion (azinphosmethyl), propargite, and demeton as alternatives to dimethoate use on pome fruits.

1. Cyhexatin. This compound has not demonstrated any adverse effects in laboratory animals in chronic feeding studies and reproduction and teratology studies.

2. Azinphosmethyl (Guthion). Both guthion and demeton are highly toxic organophosphates with acute oral LD_{50} below 20 mg/kg. Guthion was not teratogenic or fetotoxic in doses up to 5 mg/kg/day (the maternal toxic dose) in rats or mice. A recent National Cancer Institute study concluded that "under the conditions of this bioassay, neoplasms of the thyroid and pancreatic islets suggest but do not provide sufficient evidence for the carcinogenicity of azinphosmethyl in male Osborne-Mendel rats. Azinphosmethyl was not shown to be carcinogenic in female Osborne-Mendel rats or in B6C3F1 mice of either sex". The Agency is

reviewing this study and a risk assessment may be carried out based on the positive oncogenic response.

3. Propargite. This compound has not demonstrated any adverse effects in laboratory animals in chronic feeding studies and reproduction and teratology studies.

4. Demeton. See write up under Citrus above.

iii. Alternatives to Dimethoate Use on Pecans. The Agency considered phosalone and dialifor as alternatives to dimethoate use on pecans.

1. Phosalone. Phosalone is slightly more acutely toxic than dimethoate. The available data do not indicate that this compound produces adverse reproduction or teratogenic effects.

2. Dialifor. Dialifor caused no malformations in a teratology test, but the systemic NOEL was 1.0 mg/kg. The vast majority of toxicity data supporting dialifor was carried out at Industrial Bio-Test and is still unvalidated. Conclusions about the reliability of these data cannot be made at this time.

b. Comments on the Risks of Alternatives to Dimethoate. The SAP, in their formal comments, stated that it is likely that substitute pesticides which may be more hazardous than dimethoate may be selected for use in air blast equipment if dimethoate is not available.

The Cooperative Extension Service of the University of Georgia [1A(30000/16c)], in their comments on PD 2/3, stated that "while there are alternative materials (FR, p. 66560), most effective alternatives have a much higher acute toxicity than dimethoate. This particularly will effect small pecan growers and homeowners who have trees in areas where materials of high acute toxicity should not be used".

The Extension Service of Oregon State University [4(3000/16c)] and the Hood River Grower-Shipper Association, Hood River, Oregon [6(30000/16c)] stated, in their comments on PD 2/3, "Dimethoate is one of only three systemic insecticides registered for use on bearing apple trees. Of the three, dimethoate has the lowest mammalian LD_{50} toxicity at 215 mg/kg, compared to 6.2 mg/kg for demeton (Systox) and 24 mg/kg for phosphamidon. This makes dimethoate the least toxic systemic presently registered for use on apples".

American Cyanamid Co., [7(30000/16c)] commented that "should the Agency cancel air blast application of dimethoate, applications would most probably be made using parathion. This alternative would be an unacceptably high risk situation".

The Cooperative Extension of the University of California at Davis [8(30000/16c)] commented that California's treatment guide for citrus crops lists six alternatives to dimethoate for thrips control. The listed alternative materials are sabadilla, parathion, dioxathion, azinphosmethyl, phosphamidon, and ryania. This commentor stated that dimethoate, with its 4-day reentry interval, is the material of choice because a relatively safe, short-lived material is necessary for thrips control since the chemical is applied over ripe fruit.

c. The Agency's PD 4 Response. The Agency agrees that cancellation of the air blast use of dimethoate on citrus, pome fruits, and pecans may result in the air blast application of alternative pesticides registered for these same uses. The Agency is also aware that cancellation of this application method will probably not lead to the use of dimethoate on these crops by another method of application, e.g., oscillating boom sprayer. In addition, the Agency is aware that there is a high probability that, at least in some cases, the alternative pesticide may be an organophosphate of higher acute toxicity. The following key lists definitions of abbreviations used in Tables 6 and 7:

CAR - Carcinogenic effects.

CNS - Central nervous system effects - includes effects such as headaches, tremor, drowsiness, convulsions, hypnosis, anesthesia.

IHL (Inhalation) -- Inhalation in chamber, by cannulation, or through mask.

IMS (Intramuscular) -- Administration into the muscle by hypodermic needle.

INV (Intravenous) -- Administration directly into the vein by hypodermic needle.

IRP (Intraperitoneal) -- Administration into the peritoneal cavity.

LCLo (Lethal Concentration Low) -- the lowest concentration of a substance in air, other than LC50, which has been reported to have caused death in humans or animals.

LC50 (Lethal Concentration Fifty) -- a calculated concentration of a substance in air, exposure to which for a specified length of time is expected to cause the death of 50% of an entire defined experimental animal population.

LDLo (Lethal Dose Low) -- the lowest dose (other than LD50) of a substance introduced by any route, other than inhalation, over any given period of time in one or more divided portions and reported to have caused death in humans or animals.

LD50 (Lethal Dose Fifty) -- a calculated dose of a substance which is expected to cause the death of 50% of entire defined experimental animal population. It is determined from the exposure to the substance by any route other than inhalation of a significant number from that population.

NEO - Neoplastic effects.

ORAL -- Per os; intragastric, feeding, or introduction with drinking water.

PNS - Peripheral nervous system effects.

SCU (Subcutaneous) -- Administration under the skin.

SKIN -- Application directly onto the skin, either intact or abraded. Used both for systemic and primary irritant effects.

TCLo (Toxic Concentration Low) -- the lowest concentration of a substance in air to which humans or animals have been exposed for any given period of time that has produced any toxic effect in humans or produced a carcinogenic, neoplatic, teratogenic, or mutagenic toxic effect in animals or humans.

TDLo (Toxic Dose Low) -- the lowest dose of a substance introduced by any route, other than inhalation, over any given period of time and reported to produce any toxic effect in humans or to produce carcinogenic, neoplastigenic, teratogenic, or mutagenic, or mutagenic effects in humans or animals.

TER - Teratogenic effects - nontransmissible changes produced in the offspring.

TFX - Toxic effects - used to introduce the pathology or the principal organ system affected.

UNK (Unreported) -- Dose, but not route, is specified in the reference.

Table 6 summarizes the toxicological information for dimethoate and chemical alternatives to dimethoate. The information in Table 6 was derived from the "NIOSH 1978 Registry of Toxic Effects of Chemical Substances".

TABLE 6 - Summarization of toxicological information for dimethoate and chemical alternatives to dimethoate

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE															
		ORAL			SKIN	IHP		SCU		INV		IMS		IHL			UNK
		LD50	TDLo	LDLo	LD50	LD50	TDLo	LD50	LDLo	LD50	LDLo	LD50	LDLo	TDLo	LC50	LCLo	LD50
DIMETHOATE		Human 30 mg/kg															
		Rat 152 mg/kg	Rat 50 mg/kg TFX-CAR		Rat 353 mg/kg	Rat 100 mg/kg		Rat 350 mg/kg		Rat 450 mg/kg				Rat 176 mg/kg TFX-CAR			Rat 250 mg/kg
Aquatic Toxicity Rating TLm 96:10-Under 1ppm		Mouse 60 mg/kg				Mouse 45 mg/kg		Mouse 60 mg/kg									
		Dog 400 mg/kg															
		Rabbit 300 mg/kg															
		Guinea Pig 350 mg/kg			Guinea Pig 660 mg/kg												
NCI Bioassay Results Negative		Hamster 200 mg/kg						Hamster 60 mg/kg									
		Chicken 37 mg/kg															
		Mammal 15 mg/kg															
		Bird 22 mg/kg															
		Wild Bird 7 mg/kg															
				Cat 300 mg/kg													

TABLE 6 - Summarization of toxicological information for dimethoate and chemical alternatives to dimethoate (cont.)

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE															
		ORAL			SKIN	IHP		SCU		INV		IMS			IHL		UNK
		LD50	TDLo	LDLo	LD50	LD50	TDLo	LD50	LDLo	LD50	LDLo	LD50	LDLo	TDLo	LC50	LCLo	LD50
MALATHION		Rat 885 mg/kg			Rat 4444 mg/kg	Rat 340 mg/kg		Rat 1000 mg/kg		Rat 50 mg/kg							
		Mouse 775 mg/kg				Mouse 193 mg/kg				Mouse 184 mg/kg							
		Guinea Pig 570 mg/kg				Guinea Pig 550 mg/kg											
Aquatic Toxicity Rating TLm 96:10-under 1ppm		Domestic Animal 500 mg/kg															
				Human 50 mg/kg													
NCI Bioassay Results Negative				Man 857 mg/kg													
				Rabbit 120 mg/kg	Rabbit 4100 mg/kg												
																	Mammal 500 mg/kg
PHOSPHAMIDON		Rat 17 mg/kg			Rat 125 mg/kg			Rat 26 mg/kg									

TABLE 6 - Summarization of toxicological information for dimethoate and chemical alternatives to dimethoate (cont.)

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE																	
		ORAL			SKIN	IPR		SCU		IVN		IMS			IHL		UNK
		LD50	TDLo	LDLo	LD50	LD50	TDLo	LD50	LDLo	LD50	LDLo	LD50	LDLo	TDLo	LC50	LCLo	LD50
PHOSPHAMIDON (cont.) NCI Bioassay Completed 9/78		Mouse 6 mg/kg								Mouse 6 mg/kg							
		Chicken 9040 ug/kg															
		Wild Bird 2 mg/kg															
				Human 5 mg/kg													
					Rabbit 267 mg/kg												
FORMETANATE		Rat 20 mg/kg													Rat 160 mg/m^3/ 1H		
		Mouse 18 mg/kg															
		Dog 19 mg/kg															
		Chicken 21500 ug/kg															
		Bird 13 mg/kg															
					Rabbit 10200 ug/kg												

TABLE 6 - Summarization of toxicological information for dimethoate and chemical alternatives to dimethoate (cont.)

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE															
		ORAL			SKIN	IPR		SCU		IVN		IMS			IHL		UNK
		LD50	TDLo	LDLo	LD50	LD50	TDLo	LD50	LDLo	LD50	LDLo	LD50	LDLo	TDLo	LC50	LCLo	LD50
ROTENONE		Rat 132 mg/kg				Rat 2800 ug/kg	Rat 91 mg/kg TFX-NEO										
Selected by NCI for Carcinogenisis Bioassay 9/78		Mouse 350 mg/kg				Mouse 2800 ug/kg											
		Mammal 50 mg/kg															
				Human 50 mg/kg													
DEMETON		Rat 1700 ug/kg			Rat 8100 ug/kg	Rat 3 mg/kg				Rat 1750 ug/kg			Rat 3 mg/kg				
		Mouse 7800 ug/kg				Mouse 4 mg/kg	Mouse 10 mg/kg TFX-TER			Mouse 3900 ug/kg							
		Guinea Pig 9 mg/kg															
		Quail 9 mg/kg															
		Duck 7 mg/kg															
		Wild Bird 7 mg/kg			Wild Bird 1800 ug/kg												
				Human 240 ug/kg													

TABLE 6 - Summarization of toxicological information for dimethoate and chemical alternatives to dimethoate (cont.)

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE ORAL LD50	ORAL TDLo	ORAL LDLo	SKIN LD50	IRP LD50	IRP TDLo	SCU LD50	SCU LDLo	IVN LD50	IVN LDLo	IMS LD50	IMS LDLo	IMS TDLo	IHL LC50	IHL LCLo	UNK LD50
DEMETON (cont.)					Rabbit 24 mg/kg	Rabbit 3250 ug/kg											
												Dog 3650 ug/kg					
												Cat 3900 ug/kg					
MEVINPHOS		Rat 4 mg/kg			Rat 4200 ug/kg	Rat 890 ug/kg		Rat 1211 ug/kg							Rat 14 PPM/1H		
		Mouse 4 mg/kg			Mouse 4000 ug/kg	Mouse 3 mg/kg		Mouse 1180 ug/kg		Mouse 680 ug/kg							
		Chicken 7520 ug/kg															
		Wild Bird 3 mg/kg															
			Mammal 690 ug/kg TFX-PN5														
				Human 5 mg/kg													
					Rabbit 4700 ug/kg												
						Gerbil 450 ug/kg											

TABLE 6 - Summarization of toxicological information for dimethoate and chemical alternatives to dimethoate (cont.)

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE ORAL LD50	ORAL TDLo	ORAL LDLo	SKIN LD50	IRP LD50	IRP TDLo	SCU LD50	SCU LDLo	INV LD50	INV LDLo	IMS LD50	IMS LDLo	IMS TDLo	IHL LC50	IHL LCLo	UNK LD50
CYHEXATIN (Plictran)		Rat 190 mg/kg				Rat 13 mg/kg											
		Rabbit 500 mg/kg															
		Guinea Pig 780 mg/kg															
		Chicken 654 mg/kg															
				Domestic Animal 150 mg/kg													
AZINPHOSMETHYL (Guthion)		Rat 16 mg/kg			Rat 220 mg/kg					Rat 7500 ug/kg					Rat 69 mg/m^3/ 1H		Rat 15 mg/kg
		Guinea Pig 80 mg/kg															
Aquatic Toxicity Rating TLm 96:under 1ppm		Chicken 277 mg/kg															
		Wild Bird 8 mg/kg															
				Human 5 mg/kg													
NCI Bioassay Results Indefinite				Mouse 5 mg/kg	Mouse 65000 ug/kg	Mouse 5 mg/kg					Mouse 8 mg/kg						

TABLE 6 - Summarization of toxicological information for dimethoate and chemical alternatives to dimethoate (cont.)

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE															
		ORAL			SKIN	IRP		SCU		IVN		IMS		IHL			UNK
		LD50	TDLo	LDLo	LD50	LD50	TDLo	LD50	LDLo	LD50	LDLo	LD50	LDLo	TDLo	LC50	LCLo	LD50
PROPARGITE		Rat 1480 mg/kg			Rat 250 mg/kg												
PHOSALONE [mixed with Kelthane (1:2)]		Rat 600 mg/kg															
		Mouse 175 mg/kg															
DIALIFOR		Rat 5 mg/kg															
		Mouse 39 mg/kg															
		Dog 94 mg/kg															
		Rabbit 35 mg/kg			Rabbit 145 mg/kg												
				Hamster 100 mg/kg TFX-TER													
PARATHION		Rat 2 mg/kg			Rat 6800 ug/kg	Rat 1500 ug/kg					Rat 3 mg/kg			Rat 6 mg/kg		Rat 10 mg/m3/ 2H	
		Mouse 6 mg/kg				Rat 3550 ug/kg	Mouse 3500 mg/kg TFX-TER		Mouse 30 mg/kg	Mouse 17400 ug/kg				Mouse 7200 ug/kg			
		Dog 2 mg/kg								Dog 12 mg/kg							

TABLE 6 - Summarization of toxicological information for dimethoate and chemical alternatives to dimethoate (cont.)

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE															
		ORAL			SKIN	IRP		SCU		INV		IMS			IHL		UNK
		LD50	TDLo	LDLo	LD50	LD50	TDLo	LD50	LDLo	LD50	LDLo	LD50	LDLo	TDLo	LC50	LCLo	LD50
PARATHION (cont.)		Rabbit 10 mg/kg			Rabbit 40 mg/kg											Rabbit 50 $mg/m^3/$ 2H	
		Guinea Pig 8 mg/kg			Guinea Pig 600 mg/kg	Guinea Pig 12 mg/kg										Guinea Pig 14 $mg/m^3/$ 2H	
		Pigeon 3 mg/kg															
		Quail 6 mg/kg															
		Duck 2340 ug/kg															
		Domestic Animal mg/kg								Cat 3 mg/kg							Mammal 6 mg/kg
		Wild Bird 2 mg/kg			Wild Bird 1800 ug/kg												
				Human 290 ug/kg													
			Women 5670 ug/kg TFX-CNS														

TABLE 6 - Summarization of toxicological information for dimethoate and chemical alternatives to dimethoate (cont.)

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE ORAL LD50	ORAL TDLo	ORAL LDLo	SKIN LD50	IHP LD50	IHP TDLo	SCU LD50	SCU LDLo	IHV LD50	IHV LDLo	IMS LD50	IMS LDLo	IHL TDLo	IHL LC50	IHL LCLo	UNK LD50
SABADILLA		Rat 4000 mg/kg															
				Human 50 mg/kg													
						Mouse 7500 ug/kg											
DIOXATHION		Rat 20 mg/kg			Rat 63 mg/kg	Rat 30 mg/kg									Rat 1398 mg/m^3/ 1H		
		Mouse 50 mg/kg				Mouse 33 mg/kg									Mouse 340 mg/m^3/ 1H		
		Dog 10 mg/kg															
NCI Bioassay Results Negative		Guinea Pig 40 mg/kg															
		Chicken 170 mg/kg															
				Human 50 mg/kg													
	Rabbit 25 mg mild				Rabbit 85 mg/kg												

TABLE 6 - Summarization of toxicological information for dimethoate and chemical alternatives to dimethoate (cont.)

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE																
		ORAL			SKIN	IRP		SCU		INV		IMS		IHL			UNK
		LD50	TDLo	LDLo	LD50	LD50	TDLo	LD50	LDLo	LD50	LDLo	LD50	LDLo	TDLo	LC50	LCLo	LD50
RYANIA		Rat 750 mg/kg			Rat 750 mg/kg												
		Mouse 650 mg/kg															
		Dog 150 mg/kg															
		Rabbit 650 mg/kg															
		Guinea Pig 25000 mg/kg															
				Human 143 mg/kg													

Table 7 is a summary of the ranges of the toxic doses for each of the chemicals in Table 6.

TABLE 7 - Summarization of the ranges of the toxic doses of dimethoate and chemical alternatives to dimethoate

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE															
		ORAL			SKIN	IHP		SCU		IMV		IMS			IHL		UNK
		LD50	TDLo	LDLo	LD50	LD50	TDLo	LD50	LDLo	LD50	LDLo	LD50	LDLo	TDLo	LC50	LCLo	LD50
Dimethoate		7-400 mg/kg	50 mg/kg CAR	300 mg/kg	353-650 mg/kg	45-100 mg/kg		60-350 mg/kg		450 mg/kg				176 mg/kg CAR			250 mg/kg
Malathion		500-885 mg/kg		50-857 mg/kg	4100-4444 mg/kg	193-550 mg/kg		1000 mg/kg		50-184 mg/kg							500 mg/kg
Phosphamidon		9-17 mg/kg		5 mg/kg	125-267 mg/kg			26 mg/kg		6 mg/kg							
Formetanate		13-21.5 mg/kg			10.2 mg/kg												
Rotenone		50-350 mg/kg		50 mg/kg		2.8 mg/kg	91 mg/kg NEO										
Demeton		1.7-9 mg/kg		.24 mg/kg	1.8-24 mg/kg	3-4 mg/kg	10 mg/kg TER			1.7-3.9 mg/kg		3.6-3.9 mg/kg	3 mg/kg				
Mevinphos		3-7.5 mg/kg	.69 mg/kg PNS	5 mg/kg	4-4.7 mg/kg	.45-3 mg/kg		1.18-1.28		.68 mg/kg					14 PPM/1H		
Cyhexatin		190-780 mg/kg		150 mg/kg		13 mg/kg											
Azinphosmethyl		8-277 mg/kg		5 mg/kg	65-220 mg/kg	4 mg/kg				7.5 mg/kg	8 mg/kg				69 mg/m^3/1H		15 mg/kg

TABLE 7 - Summarization of the ranges of the toxic doses of dimethoate and chemical alternatives to dimethoate (cont.)

CHEMICAL	Irritant Effects (Eye)	TOXIC DOSE															
		ORAL			SKIN	IHP		SCU		IVN		IMS			IHL		UNK
		LD50	TDLo	LDLo	LD50	LD50	TDLo	LD50	LDLo	LD50	LDLo	LD50	LDLo	TDLo	LC50	LCLo	LD50
Propargite		1480 mg/kg			250 mg/kg												
Phosalone		175-600 mg/kg															
Dialifor		5-94 mg/kg		100 mgkg TER	145 mg/kg												
Parathion		2-10 mg/kg	5.6 mg/kg CNS	.24 mg/kg	1.8-600 mg/kg	1.5-12 mg/kg	3500 mg/kg TER		30 mg/kg	3-17.4 mg/kg	3 mg/kg			6-7.2 mg/kg		10-14 mg/m^3/2H	6 mg/kg
Subadilla		4000 mg/kg		50 mg/kg		7.5 mg/kg											
Dioxathion	25 mg mild	10-170 mg/kg		50 mg/kg	63-85 mg/kg	30-33 mg/kg									340-1398 mg/m^3/1H		
Ryania		150-2500 mg/kg		143 mg/kg	750 mg/kg												

The potential for exposure to the alternatives to dimethoate is an important factor in evaluating the risk from the alternatives relative to the risk from dimethoate. The Agency concludes, in a similar fashion to the conclusion in Appendix C of the Chlorobenzilate Position Document 2/3 on alternatives to chlorobenzilate's air blast use on citrus, that: (1) regardless of the pesticide used in the citrus air blast equipment, the dermal and inhalation exposure would be assumed to be similar and (2) unless the Agency had dermal penetration data to indicate otherwise, the dermal dose of these alternatives would be assumed to be similar.

The major alternatives to dimethoate use on citrus, pome fruits, and pecans are:

(1) Citrus. formetanate, malathion, phosphamidon, demeton, and mevinphos. None of these pesticides have identifiable adverse chronic or delayed toxic effects, although a complete data base is lacking for many of these compounds.

(2) Pome fruit. azinphosmethyl, cyhexatin, propargite, and demeton. Available data indicates that, with the exception of azinphosmethyl which is under review, these pesticides do not appear more hazardous than dimethoate.

Azinphosmethyl is more acutely toxic than dimethoate and, based on a recent National Cancer Institute study, may pose a carcinogenic risk. Moreover, azinphosmethyl is a restricted use pesticide and can only be used by trained pesticide applicators.

(3) Pecans. Phosalone and dialifor. Phosalone is slightly more acutely toxic than dimethoate. Agency records indicate that phosalone has been tested for oncogenicity, delayed neurotoxicity, reproductive and teratogenic effects with negative results.

Dialifor is more acutely toxic than dimethoate and has under gone the same tests as phosalone with negative results. The vast majority of toxicity data supporting dialifor, however, was carried out at Industrial Bio-Test and these data have not been validated. Therefore, conclusions concerning the reliability of these data cannot be made at this time.

Although the validity of the data concerning dialifor is in question, available data indicate that these major alternatives to dimethoate for use on citrus, pome fruit, and pecans pose at least as great a hazard as dimethaote.

Since a complete data base is lacking for many of the alternative compounds and test data for others has not been validated, the Agency cannot determine whether the risk posed by alternative chemicals will be greater than that posed by dimethoate. However, one of the factors which has led the Agency to reconsider its PD 2/3 decision to cancel the air blast use is the possibility that farmers who own air blast equipment may switch to alternative compounds which are at least as hazardous as dimethoate.

B. Comments Relating to Benefits

1. Summary of the Agency's Benefit Analysis in PD 2/3.

In assessing the benefits of the continued use of dimethoate, the Agency evaluated the economic, social, and environmental effects which would result should any or all uses of the pesticide be cancelled. The benefits of continued use were weighed against the attendant risks.

The PD 2/3 benefit analysis included a quantitative assessment of the impact of a variety of possible EPA regulatory actions on the cost of production, and the potential loss in farm income. Consumer impacts were evaluated qualitatively. The data which provided the basis for the benefit analysis were derived from information supplied by American Cyanamid, the U.S. Department of Agriculture, and other interested parties.

In Position Document 2/3, the Agency estimated annual dimethoate use at 2.8 million pounds A.I. (active ingredient) applied to about 4.7 million agricultural acres. The benefit analysis provided estimates of annual use and economic impacts of a potential cancellation action for the following classes of use sites: grains, field crops, fruits and nuts, vegetables, and other use sites.

Since comments received on the benefit analysis in Position Document 2/3 only addressed the use and benefits of dimethoate on fruits and nuts, this document will only summarize the Agency's benefit analysis for those use sites.

Dimethoate use on fruit and nut crops (apples, pears, citrus, grapes, and pecans) accounted for about 839,000 pounds AI applied to about 533,000 acres. The percent of total U.S. acreages treated with dimethoate were 2.6 percent for apples, <1.0 percent for pears, 12.0 percent for citrus, and 17.0 percent for pecans. About 58 percent of the California grape acreage was treated with dimethoate.

For apples, pears, and pecans several effective alternatives for dimethoate are available; the efficacy and performance of alternatives for grapes and citrus are limited. If dimethoate were cancelled total estimated production cost increases for these crops are $89,700 for apples, at least $551,000 for citrus, $3.9 - $10.7 million for grapes, and $745,800 for pecans. Since only minor amounts of dimethoate are used on pears, the cancellation of dimethoate for this use would have negligible effects upon total production costs.

Changes in the value of production would either be negligible or not expected for apples, pears, and pecans. Annual grape production losses in California, of $40,800 are expected from vine losses due to insects commonly referred to as sharp shooters. Significant adverse effects on the quantity and quality of citrus production are possible; however, data were not available to evaluate the economic magnitude of such effects.

Estimated decreased farm incomes for apples and pecans are, respectively, about \$90,000 and \$745,800 (or \$7.00 and \$14.34 per impacted acre). For citrus, the farm loss could exceed \$551,000, or at least \$3.58 per impacted acre (significant quality losses due to thrips damage could not be assessed with available data). The decreased farm income for impacted grape producers would be \$3.94 - \$10.74 million, or \$12.55 - \$34.22 per acre; total insecticide use would increase. Farm income effects for all pear producers would be negligible; income effects on an impacted acre basis could not be estimated.

Even though significant economic impacts would be experienced by some U.S. fruit and nut producers (e.g., \$3.94 - \$10.74 million for grape growers, \$745,800 for pecan growers, etc.), consumer impacts are not expected for pears and apples due to the small proportion of the total U.S. production affected. Price increases may occur for pecan, citrus and grape products; but these increases are qualitatively not expected to be of major significance. Consumer impacts could not be quantitatively estimated due to the lack of data.

2. Summary and Analysis of Comments Received in PD2/3--a. Air Blast Application of Dimethoate for Citrus, Pome Fruit, and Pecans--i. Comments on the Need for and Extent of Air Blast Application for Citrus, Pome Fruit, and Pecans. Several commenters addressed the use and benefits of air blast application of dimethoate on citrus, pome fruit, and pecans as follows:

The College of Agriculture of the University of Arizona [5(30000/16c)] commented that most (90%) of the applications of dimethoate on citrus are by air blast ground spraying and many new sprayers were purchased in 1978 and 1979. Aerial application, continued the commenter, does not provide adequate canopy penetration, requiring a second aerial application a few days later, thus doubling costs and the amount of insecticide used as well as increasing exposure.

The California Citrus Quality Council [9(30000/16c)] indicated that air blast application of dimethoate is the predominant application method in California for control of aphids and citrus thrips.

The University of California Extension Service at Davis [8(30000/16c)] submitted extensive comments on the need for and extent of use of dimethoate and of air blast equipment for citrus. They estimated that in the San Joaquin Valley, 70% of first applications for trip control on citrus are dimethoate applied with air blast equipment. This commentor further stated that air blast equipment is used almost exclusively in the treatment of apples, pears, and other fruit and nut crops in California. Note was made that the pear and apple crops use much less dimethoate than the citrus crops.

The University of California at Davis also stated that air blast equipment in many cases is preferred over aerial application and is steadily replacing fixed and even oscillating boom sprayers for fruit and nut tree crops. The reasons for preferring air blast equipment include speedier application times which enables better timing of applications, lower volumes while maintaining efficacy, lesser amounts of active ingredient, lower application costs, and better coverage.

The Cooperative Extension Service of the University of Georgia [1(30000/16c)] indicated that "virtually all pesticide applications to [pome fruit in Georgia] are made with air blast sprayers." The Georgia Extension Service in Tifton, Georgia [1A (30000/16c)], also emphasized that the prohibition of dimethoate air blast applications would be the same as cancellation of the chemical for pome fruits and pecans in Georgia.

William R. Gale [3(30000/16c)] indicated that 98% of the commercial use of dimethoate on pome fruits is by air blast equipment.

Oregon State University Extension Service [4(30000/16c)] commented that "practically all commercial applications of pesticides in apple orchards, including dimethoate, are made by air blast sprayer." Prohibiting the use of dimethoate by air blast equipment would virtually eliminate its commercial use in this area.

The Hood River Grower-Shipper Association [6(30000/16c)] repeated the concerns of the Oregon State Extension Service.

The College of Agriculture of the University of Idaho [10(30000/16c)] indicated that "a relatively small percentage of Idaho apple and pear acreage is treated with dimethoate, since insecticides which do not reduce predator mite populations are usually preferred." However, they stated that virtually all pesticide application in Idaho commercial orchards is by air blast equipment. They also discussed alternate application methods, including aerial, hand gun spraying, oscillating boom sprayers, and overhead sprinklers, and concluded that "air blast application has definite advantages in efficacy, economy, and, in some instances, safety."

The Cooperative Extension Service of Washington State University [11(30000/16c)] commented that virtually all applications of dimethoate on apples in central Washington is by air blast equipment. Prohibiting the use of dimethoate in air blast equipment would virtually eliminate the use of the chemical on apples in central Washington.

ii. The Agency's PD 4 Response. None of the comments provided specific new information that causes the Agency to revise its original estimates on the economic benefits of dimethoate or the economic impact of cancelling dimethoate use on citrus, pome fruit, and pecans. The Agency was unable to estimate the quality or yield losses due to a lack of necessary data. The $551,000 economic impact on citrus growers, estimated in PD 2/3, is an increase in costs. Output effects could not be measured. Therefore the Agency's original estimate of the economic benefits of dimethoate use on citrus, pome fruit, and pecans remains unchanged. The comments do emphasize, however, the extensive use of air blast application on these crops, and the Agency agrees with the commenters that air blast appears to be the predominant mode of application of dimethoate for the control of certain insect pests on these crops.

The University of Arizona argued that aerial application to citrus requires a second application compared to air blast. From this argument one would presume that air blast only requires a single application. The Univeristy of California however, estimated "that in the San Joaquin Valley, 70% of the first applications of dimethoate for thrips control on citrus are applied with air blast equipment". This statement would lead one to believe that a second application is required, at least in the San Joaquin

Valley. The Agency re-reviewed the information in the USDA/EPA Assessment Team Report on Dimethoate. A summary of the number of applications of dimethoate to citrus by aerial and ground application indicates that on an average 1 to 2 applications of the pesticide, whether applied by ground equipment or by aerial application, are made to citrus crops.

b. Citrus--i. Comments on Air Blast Application of Dimethoate for Control of Aphids and Citrus Thrips. The College of Agriculture of the University of Arizona [5(3000/16c)] commented that dimethoate use in Arizona is almost exclusively confined to citrus, some for the control of aphids, but most for citrus thrips. The commenter stated that 90% of the applications of dimethoate are by air blast ground spraying. Aerial application, continued the commenter, does not provide adequate canopy penetration, requiring a second aerial application a few days later, thus doubling costs and the amount of insecticide used as well as increasing exposure.

ii. The Agency's PD 4 Response. The Agency agrees with the commenter that ground application of dimethoate, whether it be boom sprayer or air blast sprayer, does tend to give better penetration of the canopy of citrus trees than does aerial application. The Agency also agrees that for stem feeding pests, such as mites and scale insects, applications that penetrate the canopy are more effective. However, where the pest is a peripheral feeder, such as terminal feeding aphids or thrips, aerial applications can be used and are used when conditions do not permit utilizing air blast equipment.

Thus, this comment provides no specific new information that causes the Agency to revise its original estimates on the economic benefits of dimethoate use on citrus.

c. Pome Fruits--i. Comments on the Use of Dimethoate for Control of Rosy Apple Aphids. William R. Gale [3(30000/16c)] commented that the states of Oregon and Washington need dimethoate for control of rosy apple aphids for occasions when other insesticides will not work.

Oregon State University Extension Service [4(30000/16c)] commented that:

> Insecticides for rosy apple aphid control in the spring are often mixed with fungicides for disease control. Tank mixing of water-dispersible powders with emulsifiable concentrates containing petroleum solvents often causes phytotoxicity to fruit and foliage. Dimethoate is the only systemic aphicide in a water-dispersible formulation which may be more safely applied as a tank mix with water-dispersible fungicides.

> Control of rosy apple aphid and woolly apple aphid is often difficult due to the difficulty of contacting the insects. Rosy apple aphids distort and roll leaves and are protected from wetting in the rolled leaves, while woolly aphid aerial colonies secrete a cottony wax over their bodies which repels water sprays. In controlling these species, it is often necessary to use a systemic insecticide such as dimethoate applied thoroughly to the foliage by ground dispersal equipment. Dimethoate is needed as a necessary alternative in control of these pests in commercial apple orchards.

ii. The Agency's PD 4 Response. The Agency agrees with these commenters on the usefulness of dimethoate in controlling the rose apple aphids. The Agency is not proposing to cancel the use of dimethoate on apples. Moreover, the Agency has decided not to pursue cancellation of air blast application at this time. The Agency will re-assess its decision on the air blast use when the results of exposure studies are received and evaluated.

iii. Comments Regarding the Registration of Phosphamidon Having Been Withdrawn. The Cooperative Extension Service of Washington State University [11(30000/16c)] forwarded comments from its Tree Fruit Research Center indicating the increased need for dimethoate on apples, since the registration of phosphamidon, a widely-used insecticide for aphids and white apple leafhopper, has been withdrawn.

iv. The Agency's PD 4 Response. The Agency does not have any information indicating that the registration of phosphamidon has been withdrawn. A check of the records indicates that phosphamidon is still registered with the Agency and would therefore be allowed for use.

d. Pecans--i. Comments on the Impact of A Minor Increase in the Cost of Pecan Production. The Cooperative Research Service of the University of Georgia at Athens [1(30000/16c)] and at Tifton [1A(30000/16c)] commented that "While the effects of cancellation might be negligible or slight on a nationwide basis (FR, p. 66560), a minor increase in the cost of production might mean the difference in whether or not some small pecan growers can economically manage their arthropod pests".

ii. The Agency's PD 4 Response. In PD 2/3 the Agency had estimated decreased farm income for pecans would be $14.34 per impacted acre if dimethoate were cancelled for use on pecans. However, the Agency's proposal was not to cancel the use of dimethoate but rather to prohibit one particular application method. Dimethoate would have still been available for use on pecans but by a mode of application other than air blast. In addition, phosalone and dialifor are available as alternatives to dimethoate. The use of dimethoate with an alternative mode of application or the substitution of the alternative compound would only result in a minor increase in the cost of production. Although this slight cost increase might have an impact on some small pecan growers, the Agency does not believe in general such an impact would be substantial at the user level.

C. Comments Relating to Regulatory Options

1. Summary of the Agency's Regulatory Options in PD 2/3. The development of the regulatory options designed to reduce the risks accompanying the use of dimethoate focused on means to reduce the level of human exposure to dimethoate. In addition to dietary exposure, individuals may be exposed to dimethoate before or during application. Before application, mixers and loaders may be exposed both dermally and via inhalation as the result of splashing, vaporization, or accidental spills; during application, pilots and flaggers involved in aerial application, as well as ground applicators, may all be exposed both dermally and via inhalation.

The Agency considered each of these exposure situations, and identified several categories of regulatory options which include various methods of risk reduction. Those regulatory options considered were as follows:

(1) Continue registration of all uses without restriction.

(2) Continue registration of all uses without restriction but require additional oncogenicity, mutagenicity, and delayed neurotoxicity studies.

(3) Continue registration of all uses but (a) require additional oncogenicity, mutagenicity, and delayed neurotoxicity studies, and (b) amend the terms and conditions of certain registrations.

(4) Continue registration of all uses but (a) require additional oncogenicity, mutagenicity, and delayed neurotoxicity studies, (b) amend the terms and conditions of certain registrations, and (c) require comprehensive studies to determine the amount of exposure incurred during all air blast application situations.

(5) Continue the registration of most uses but (a) require additional oncogenicity, mutagenicity, and delayed neurotoxicity studies, (b) amend the terms and conditions of certain registrations, (c) require comprehensive studies to determine the amount of exposure incurred during all air blast situations, and (d) cancel the use of all dust formulations.

(6) Continue registration of most uses but (a) require additional oncogenicity, mutagenicity, and delayed neurotoxicity studies, (b) amend the terms and conditions of certain registrations, (c) specifically prohibit the use of air blast equipment when treating citrus, pecans, and pome fruit, (d) require comprehensive studies to determine the amount of exposure incurred during all air blast situations not covered in (c) above, (e) specifically warn female workers involved in air blast application practices of the potential teratogenic effects of dimethoate, and (f) cancel the use of all dust formulations.

(7) Cancel all uses.

In PD 2/3 the Agency proposed adoption and implementation of regulatory option number 6 above. This option was selected because it represented the best available course of action for reducing or eliminating applicator exposure and concurrent risk while maintaining a generally high level of benefits and for gathering additional toxicological data needed to better evaluate risk. In adopting this option the Agency proposed to take regulatory action in three general areas: 1) generation of additional data; 2) modifying the terms and conditions of registration for the uses of dimethoate; and 3) cancellation of selected high risk application practices and high risk formulations.

2. Summary and Analysis of Comments Received in PD 2/3--a. Cancel Dust Formulations--i. Summary of the Agency's Conclusions in PD 2/3. In Position Document 2/3 the Agency concluded that the risk resulting from the use of dust formulations of dimethoate outweighed the benefits derived from the use of the dust formulations. Dimethoate in the form of a wettable powder is the choice alternative to the dust formulation. Because the wettable powder formulation results in lower applicator exposure, the total risk for the wettable powder formulation would be less than that of the dust formulation. The Agency, therefore, proposed eliminating the use of all dust formulations of dimethoate. The dust formulations are intra-state labels for which applications for Federal Registration are pending. Intra-state applicants who have previously submitted a Notice of Application for Federal Registration are permitted to sell and distribute affected pesticide products solely in intra-state commerce, pending a final decision concerning Federal Registration.

ii. Comments on the Elimination of Dust Formulations. The U.S. Department of Agriculture and the Scientific Advisory Panel agreed, in their comments, with the Agency's decision to eliminate the registration for dust formulations of dimethoate in order to reduce applicator risk.

iii. The Agency's PD 4 Response. The Agency will proceed with its proposed elimination of the use of all dust formulations of dimethoate.

b. Require Protective Clothing and Equipment--i. Summary of the Agency's Conclusion in PD 2/3. In Position Document 2/3, the Agency concluded that potential mutagenic and reproductive/teratogenic risks are too high relative to the benefits associated with the use of dimethoate. However, the Agency also concluded that the benefits of dimethoate use would outweigh the risks, if specific changes in application practices were implemented to reduce dermal and respiratory exposure. The Agency, therefore, proposed the requirement of protective clothing for applicators of all dimethoate products and for all uses of dimethoate, and the requirement of respirators for pilots and mixer/loaders.

ii. Comments on Requiring Protective Clothing for Applicators of All Dimethoate Products and All Uses. The Agency received several comments relating to the recommendation to require protective clothing for all products and all uses.

The Department of Agriculture, in their comments supports the modification of labeling to include protective clothing and equipment for applicators.

American Cyanamid [7(30000/16c)] commented that a significant benefit in reducing exposure can be achieved through the use of protective clothing and for certain uses is preferred. For certain uses, however, American Cyanamid contended that this requirement is an extra precaution that will not significantly increase the margin of safety. The commenter cites CYGON® 2E systemic insecticide formulations for fly vector control and insect control on ornamental plants as an example. American Cyanamid stated that the margin of safety as calculated by the EPA, for the fly vector control use is 1,474 and that this is achieved without discomforting the applicator with rubber gloves, boots, etc. Protective clothing for this use raises the margin of safety to 3,111. American Cyanamid stated that although protective clothing is advisable, its requirement in this case is arbitrary.

American Cyanamid also stated that for other uses simple devices such as a canvas covering for the applicator area on the rig may be preferable to protective clothing and that in excessively hot temperatures applicators would more likely exercise this safety precaution than they would the use of protective clothing.

The Nebraska Aviation Trades Association [2(30000/16c)] stated that the required protective clothing would hinder the pilots in flying the aircraft, and that the use of closed mixing and loading equipment would make this requirement unnecessary for applicators.

The California Citrus Quality Council [9(30000/16c)] also stated that the use of closed mixing and loading equipment would obviate the need for protective clothing, and that drivers are exposed only to the diluted spray material and are, in addition, protected by cab enclosures or other protective provisions.

iii. The Agency's PD 4 Response. In Position Document 2/3 the Agency calculated the MOS for the various uses of dimethoate from the estimated exposure for those uses. The assumptions which were made in order to arrive at the exposure estimates, and thus, to calculate the MOS are stated in Position Document 2/3. Table 8 shows the Agency's calculations of applicator exposure and margins of safety for various uses of dimethoate under curent practices (no protective clothing and equipment) and with protective clothing and equipment.

TABLE 8 - Applicator exposure and margins of safety for various users of dimethoate excluding dietary (oral) exposure 1/

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE	MOS UNDER CURRENT PRACTICES 2/	EXPOSURE (DERMAL AND INHALATION WHEN PROTECTIVE CLOTHING IS REQUIRED)	MOS WHEN PROTECTIVE CLOTHING IS REQUIRED	TOTAL EXPOSURE WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED	MOS WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQURIED
corn	air	pilots	0.0083	337	0.00806	347	0.00086	3,256
corn	air	flaggers	0.008	350				
corn	air	mixers/loaders	0.0063	444	0.0043	651	0.00088	3,182
ornamental	ground	commerical high concentration compressed air	0.00012	23,333	0.000037	75,676	0.00002	140,000
ornamental	ground	home garden high concentration	0.000152	18,421	0.000045	62,222	0.00003	93,330
grape	ground	Boom highest conc.	0.0012	2,333	0.0004	7,000	0.00023	12,174
grape	ground	highest conc. (custom) Copplestone model	0.0207	135	0.006	467	0.0038	737
grape	ground	dust	0.130	22 3/	0.130	22	0.013	215
cotton	air	pilots	0.0017	1,647	0.0016	1,759	0.00017	16,471
cotton	air	mixers/loaders	0.0095	295	0.00065	4,308	0.00014	20,000
cotton	ground	applicators	0.0078	359	0.0024	1,167	0.00145	1,931
cotton	ground	mixers/loaders	0.00033	8,485	0.00011	25,454	0.00007	40,000
citrus	air	pilots, ground crews, mixers/loaders	same as corn					

1/ This table was Table VII in Position Document 2/3.

2/ Based on a 2.8 mg/kg NOEL (Khera unpublished).

3/ Exposure is via inhalation .

TABLE 8 - Applicator exposure and margins of safety for various users of dimethoate excluding dietary (oral) exposure[1] (cont.)

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE	MOS UNDER CURRENT PRACTICES[2]	EXPOSURE (DERMAL AND INHALATION WHEN PROTECTIVE CLOTHING IS REQUIRED)	MOS WHEN PROTECTIVE CLOTHING IS REQUIRED	TOTAL EXPOSURE WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED	MOS WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQURIED
citrus	ground (air blast model)	applicators[4] mixers/loaders	0.39	7	0.078	36	0.071	39
sorghum	air	same as corn						
veg. fields (tomato, broccoli)	air	pilots	0.013	215	0.0128	219	0.014	2,000
		flaggers	0.013	215				
		mixers/loaders	0.0062	452	0.0043	651	0.00088	3,182
veg. (Fla)	ground	applicators	0.00005	56,000	0.00001	280,000	0.000007	400,000
vector control (house fly)	ground	applicators	0.0019	1,474	0.0009	3,111	0.00032	8,750
forest pine (seed orchard)	ground	applicators	0.0008	3,500	0.00025	11,200	0.00014	20,000
pecan	ground (air blast)	applicators mixers/loaders	0.119	24	0.0252	111	0.0232	121
safflower	air	same as corn						
pome	ground (air blast model	commercial applicators including mixers/loaders	0.242	12	0.0527	53	0.0485	58
pome	ground	hose sprayers	0.00017	16,471	0.00005	56,000	0.000032	87,500

[1] This table was Table VII in Position Document 2/3.

[2] Based on a 2.8 mg/kg NOEL (Khera unpublished).

[4] Applicator is also mixer/loader.

TABLE 8 - Applicator exposure and margins of safety for various users of dimethoate excluding dietary (oral) exposure[1] (cont.)

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE	MOS UNDER CURRENT PRACTICES[2]	EXPOSURE (DERMAL AND INHALATION WHEN PROTECTIVE CLOTHING IS REQUIRED)	MOS WHEN PROTECTIVE CLOTHING IS REQUIRED	TOTAL EXPOSURE WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED	MOS WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED
soybean	air	same as corn						
wheat	air	same as corn						
tobacco high conc.	ground	applicators including mixers/loaders	0.00042	6,667	0.00013	21,538	0.00008	35,000
alfalfa High conc.	ground	applicators including mixers/loaders	0.00052	538	0.00163	1,718	0.00097	2,887
veg. fields (lettuce)	ground	applicators	0.0002	14,000	0.00007	40,000	0.000043	65,116
		mixers/loaders	0.00026	10,769	0.00009	31,111	0.000054	51,852

1/ This table was Table VII in Position Document 2/3.

2/ Based on a 2.8 mg/kg NOEL (Khera unpublished).

From Table 8 we can see that there are certain use situations where, based on these exposure estimates, protective clothing would not significantly increase the estimated margin of safety. The Agency would therefore tend to agree, to a certain extent, with American Cyanamid's comments that for certain uses the MOS would not substantially increase with protective clothing. However, it would not only be impractical but nearly impossible to develop labeling to show all the various use areas and/or conditions where protective clothing would and would not significantly increase the margin of safety for the applicator.

With regard to American Cyanamid's contention that simple devices such as canvas coverings for the applicator area on the rig are preferred by applicators in excessively hot weather, the Agency would also tend to agree with American Cyanamid. However, in the absence of field data measuring the efficacy of such devices in reducing exposure to applicators, the Agency will proceed with requiring protective clothing, but encourages the development of field data for such devices. The Agency would be receptive to modifying labeling if data showing the risk reducing potential of this method are provided.

Therefore, while it agrees to some extent with American Cyanamid, the Agency will require the use of protective clothing for all uses. However, pilots will not be required to wear protective clothing while engaging in flying the aircraft. The Agency has re-evaluated the requirements for protective equipment and clothing for aircraft pilots and has decided that protective clothing and equipment would in itself be a hazard to pilots engaged in flying the aircraft. Pilots will not therefore be required to wear protective clothing and equipment while flying the aircraft, however the Agency encourages the use of aircraft equipped with positive ventilation equipment. Pilots involved in the mixing-loading operation will be required to wear protective clothing and equipment during that operation.

With regard to the comments of the California Citrus Quality Council on mixer/loader exposure and protective clothing, the Agency does not feel that the efficacy of closed mixing and loading systems have thus far demonstrated that they would obviate the need for protective clothing. Recent industry submissions on closed systems suggest that protective clothing may not be necessary, however, field monitoring studies need to be carried out to determine the level of exposure to applicators using this type of equipment. In the meantime the Agency will require protective clothing even for closed mixing and loading systems.

c. Require Automatic Flagging--i. Summary of the Agency's Conclusion in PD 2/3. In Position Document 2/3, the Agency determined that the potential risks to human flaggers are too high relative to the benefits associated with the use of dimethoate. Therefore, the Agency proposed to eliminate the risk by requiring the use of automatic flagging equipment for all aerial application situations.

ii. Comments Opposing the Use of Automatic Flagging Devices. The Scientific Advisory Panel (SAP), in their comments, objected to the proposed prohibition of the conventional use of human flaggers to mark swaths in aerial spraying and the associated requirement for use of automatic flagging devices. The Panel stated that insufficient research has been accomplished to indicate that the technique would be an effective regulatory procedure to reduce risks to man and the environment. The Panel recommended that the Agency determine the limitations of automatic flagging in various agricultural situations before making the use of these devices an absolute requirement. The Panel also encouraged the Agency to promote research on flagging devices to expedite their development and availability to farmers.

The Department of Agriculture suggested, in their formal comments, that the Agency not prohibit the use of human flaggers, but require protective clothing and equipment to minimize any exposure the flaggers may experience. The Department of Agriculture also recommended additional studies of actual exposure of all workers during aerial application.

American Cyanamid [7(30000/16c)] suggested alternative labeling requiring human flaggers to use "proper flagging techniques to avoid exposure from drift." Cyanamid added that the use of automatic flag paper dispensers must be discontinued after the plants reach a height that makes it difficult to see the paper. They further urged the Agency to accept the analysis and comments presented by the National Agricultural Aviation Association at the SAP meeting regarding automatic flagging.

Mr. Harold Collins, Director of the National Agricultural Aviation Association made a presentation before the Scientific Advisory Panel on November 29, 1979, in which he addressed the recommendation that automatic flagging equipment be used to the exclusion of ground flaggers.

Mr. Collins stated that automatic flagging equipment is expensive, and that some types can cost as much as $50,000 per aircraft. There are less expensive flagging devices than the $50,000 device, but many of these become impractical or unusable later in a spray season. Mr. Collins further commented that the "ag" aircraft industry would find it inappropriate to even continue spraying dimethoate in some situations if they were required to go to equipment that is as expensive as $50,000.

Mr. Collins questioned the necessity to eliminate the possibility of flagging since there are methods of human flagging which are acceptable which should minimize the potential exposure.

Mr. Collins stated that there are circumstances that make automatic flagging systems impractical. For example, a system which uses paper is designed to mark the last or the edge of the last spray run (or the end of a spray run midfield) becomes impractical as the crop matures and obscures the paper from view. Automatic flagging is not necessarily adequate until you get into equipment like the electronic equipment which is accurate to about five meters at the current time. However, these electronic devices are a new and innovative aid, and they are very expensive.

Mr. Collins commented that if it was found that protective clothing was required with dimethoate use, he did not believe that the National Agricultural Aviation Association would object to it.

The University of California (8(30000/16c)) commented that the technology for efficient mechanical flagging or marking is not well-advanced. They stated that proper protective clothing and equipment might reduce the exposure to persons serving as flaggers for aerial application.

The California Citrus Quality Council (9(30000/16c)) commented that "practical procedures for automatic flagging have not been adequately developed and have not been generally adopted by licensed pilots and their organizations.... (P)rovision should be made for the continued use of workers as flaggers, since, properly positioned and protected, they are not at untenable risk in this occupational exposure."

iii. The Agency's PD 4 Response. The Agency has decided not to prohibit the use of human flaggers during aerial application of dimethoate, but to encourage the use of automatic devices, when feasible. When human flaggers are used, precautions, such as the wearing of protective clothing, will be required to minimize the exposure of applicators to dimethoate.

d. Prohibit Air Blast Application on Citrus, Pome Fruits, and Pecans--i. Summary of the Agency's Conclusions in PD 2/3. In Position Document 2/3, the Agency concluded, in the case of the citrus, pome fruits, and pecan uses of dimethoate, that the use of available protective clothing and equipment will not reduce the risk experienced by applicators using air blast equipment to an acceptable level. The Agency, therefore, proposed the prohibition of air blast application equipment when treating citrus, pome fruits, and pecans with dimethoate.

In Position Document 2/3, the Agency projected that if air blast application of dimethoate on citrus were cancelled, some dimethoate users would use aerial application, a few might switch to other ground application techniques, and some would use alternate pesticides. Because of a lack of data it was not possible to determine the relative adoption ratios of these three strategies and their associated economic impacts. Thus, the impact of restricting air blast application was estimated to range from zero impact to the same impact as cancellation (more than $551,000/year). Yield and quality losses were not considered in the $551,000 impact.

ii. Comments on Exposure with of Air Blast Application for Citrus, Pome Fruit, and Pecans Compared to Alternative Application Techniques Compared to Alternative Application Techniques. The Agency received comments on this proposed regulatory action from the Scientific Advisory Panel, U.S. Department of Agriculture, University of Georgia [1(30000/16c)], William R. Gale of Oregon [3(30000/16c)], Oregon State University [4(30000/16c)], University of Arizona [5(30000/16c)], Hood River Grower-Shipper Association [6(30000/16c)], American Cyanamid [7(30000/16c)], University of California [8(30000/16c)], California Citrus Quality Council [9(30000/16c)], University of Idaho [10(30000/16c)], and Washington State University [11(30000/16c)].

The California Citrus Quality Council [9(30000/16c)] commented that the definition of air blast equipment, provided in the Federal Register, is not adequate or useful, since the exposure of the applicator is central to the issue, not the operating pressure and spray volume. A functional definition proposed by the Council characterizes air blast equipment for tree crops as that application method which uses a directionalized air stream with velocities of 50 miles per hour (m.p.h.) or greater to move entrained spray droplets towards a target area.

The University of California at Davis [8(30000/16c)] also proposed a definition of air blast equipment based on velocity of the air stream, not on pressure or volume.

The California Citrus Quality Council [9(30000/16c)] further commented that air blast applicators with a variety of conditions of pressure, velocity, and volume do not invariably provide greater applicator exposure than application with manual equipment or with stationary or oscillating booms. Variations in exposure relate more to ground speeds, the direction, magnitude, and constancy of natural air movement of the equipment, humidity/temperature factors, etc., than to the type of equipment. The Council predicted, in fact, that the greatest potential for exposure was in manual ground spraying and that oscillating booms with their recurrent forward sweep of the spray pattern, slower ground speeds, and broader range of droplet size have greater potential for exposure than air blast units which involve faster ground speeds and more forcibly project the spray into the target area at a set angle of 90 degrees in relation to the movement of the equipment. Applicator exposure could be minimized, according to the Council, by using simple canopies or cab enclosures.

Finally, the California Citrus Quality Council supported applicator exposure studies underway in California and indicated that, unless such exposure studies show the exposure to be substantial and not reducible by simple canopies or cab enclosures, that the citrus growers would protest the prohibition of air blast application of dimethoate.

iii. The Agency's PD 4 Response. All of the comments received by the Agency on this issue disagreed with the recommended option to cancel the air blast use of dimethoate for citrus, pome fruits, and pecans. However, none of these comments contained any new information regarding application exposure resulting from this use of dimethoate. Many of the comments recommended that field monitoring studies be carried out in order to refine the Agency's exposure estimates.

The Agency agrees that additional data is necessary to refine the Agency's exposure estimates for the air blast uses of dimethoate. In the absence of appropriate data to adequately compare applicator exposure from the use of air blast equipment with the exposure resulting from other application methods, such as the oscillating boom sprayers, the Agency believes that the cancellation of the air blast use is premature. Hence, the Agency has reconsidered its position and will not cancel the airblast use of dimethoate at this time.

This conclusion is supported by information indicating that a large number of farmers perfer the use of air blast equipment, and own such equipment. Hence, they are likely to use substitute pesticides which may be at least as hazardous as dimethoate with this air blast equipment if dimethoate is not available. The Agency also recognizes that dimethoate is a valuable pesticide component of integrated pest management (IPM) programs for citrus insect pests and that such programs are almost totally based around the use of air blast equipment to apply reduced dosages and selective coverage. In view of these considerations, the Agency will retain the air blast use at this time. The Agency will, however, require the submission of exposure information in accordance with the protocols and timetables set forth in Chapter III of this document, and will use this data, in conjunction with any other available information, to re-assess the exposure potential of the air blast method and the attendant risks posed to humans.

e. Warning Statement for Female Applicators--i. Summary of the Agency's Conclusion in PD 2/3. In Position Document 2/3, the Agency stated its concern for women applicators applying dimethoate via air blast equipment during pregnancy. The Agency proposed to require that all products containing dimethoate which can be or are intended to be used with air blast equipment must bear a statement on the label warning female workers that dimethoate causes birth defects in laboratory animals. The label warning proposed by the Agency reads as follows:

> Warning to Female Workers (in 16 pt. Red lettering)
>
> The United States Environmental Protection Agency has determined that dimethoate, an active chemical ingredient in this product, causes birth defects in laboratory animals. Exposure to this product during pregnancy should be avoided.

ii. Comments on Requiring a More Direct Warning. The Department of Agriculture suggested that a more direct warning such as "Pregnant women should avoid exposure", be used to alert female workers using air blast equipment of possible hazards resulting from exposure to dimethoate during pregnancy.

iii. The Agency's PD 4 Response. The label warning statement proposed by the Agency in PD 2/3 concludes with the statement: "Exposure to this product during pregnancy should be avoided". The Agency believes this statement is a sufficiently direct warning, however the Agency has decided not to require this label modification.

iv. Comments Urging the Agency to Withdraw the Requirement for a Warning Statement to Female Applicators. American Cyanamid [7(30000/16c)] recommended that the Agency withdraw the requirement for a warning statement to female applicators. In the opinion of American Cyanamid, the requirement is not supported by the facts in Dr. Khera's paper and a warning statement describing other than acute hazards would represent a change in the Agency's policy. American Cyanamid also stated that the Science Advisory Panel rejected the teratology warning statements on labels.

v. The Agency's PD 4 Response. The Agency has decided to drop the requirement for a warning statement to female applicators. This decision was based on the Agency's conclusion that the available data on teratogenicity does not indicate that dimethoate poses a significant teratogenic risk. Therefore, because of the limited extent of our data at this time the Agency will not require a warning to female applicators.

D. Comments Relating to Testing Requirements

1. Summary of the Agency's PD 2/3 Position. In Position Document 2/3 the Agency identified several areas requiring additional testing and directed registrants to submit the data discussed below.

a. Oncogenicity. The Agency determined that available evidence for oncogenicity is suggestive and warrants further study. Therefore, the Agency directed registrants to conduct an oncogenicity bioassay using dimethoate in the same strain of mice and rats as that of the Gibel study. The Agency stated that this study shall be completed and submitted within three years of the Agency's final determination (Position Document 4) for dimethoate. The Agency further stated that protocols for this oncogenicity bioassay shall be submitted to the Agency within 90 days of receipt of the Agency's final Notice of Determination (PD 4) for dimethoate.

b. Mutagenicity. The Agency also determined that insufficient data exists upon which to base a mutagenicity risk assessment. The Agency concluded that additional testing is required. Therefore, the Agency directed registrants to provide adequate test data concerning dimethoate's ability to cause gene mutation in animal cells. The Agency stated that registrants shall also conduct a dominant lethal study in mice as well as studies designed to detect spindle effects which may result in numerical chromsomal aberrations. Protocols for these studies shall be submitted to the Agency within 90 days of receipt of the Agency's final Notice of Determination for dimethoate. Tests shall be completed and submitted within eighteen (18) months of receipt of the Agency's final Notice of Determination for dimethoate. The Agency also stated that further testing may be required based on the results of the studies discussed above in order to properly evaluate mutagenic potential and/or risk.

c. Delayed Neurotoxicity. The Agency determined that insufficient data are available to determine whether dimethoate can induce delayed neurotoxic effects. Therefore, the Agency directed registrants to conduct appropriate neurotoxicity testing in accordance with the final registration guidelines. Protocols for these studies shall be submitted to the Agency within 90 days of receipt of the Agency's final Notice of Determination for dimethoate. These test shall be completed and submitted within eighteen (18) months of receipt of the Agency's final Notice of Determination for dimethoate.

d. Applicator Exposure Data. The Agency determined that there is insufficient applicator exposure data concerning air blast application situations to determine whether there are sufficient margins of safety for reproductive/teratogenic effects. The Agency directed registrants to conduct appropriate field studies to determine worker exposure (dermal and inhalation) during application of dimethoate using air blast type application equipment. Registrants shall gather such data for each crop where air blast equipment is used or on crops deemed representative of such applicator exposure situations. Registrants shall submit proposed test protocols for gathering applicator exposure data to the Agency within

90 days of receipt of the Agency's final Notice of Determination for dimethoate and shall complete all such tests and submit all exposure data to the Agency within 18 months of receipt of the Agency's final Notice of Determination for dimethoate.

2. Summary and Analysis of Comments Received on PD 2/3--a. Oncogenicity Testing--i. The Agency's Position on PD 2/3. In Position Document 2/3, the Agency concluded that additional data were required concerning the oncogenic potential of dimethoate.

ii. Comments Objecting to Additional Oncogenicity Testing. The Scientific Advisory Panel (SAP), in its formal comments, objected to this additional testing requirement, stating that the negative NCI bioassay, flawed though it is, in conjunction with a lack of carcinogenicity of organic phosphate pesticides in general, makes further testing of dimethoate unnecessary.

American Cyanamid [7(30000/16c)] supported the SAP position against further oncogenicity testing.

iii. The Agency's PD 4 Response. The Agency's Cancer Assessment Group (CAG), in a recent review (Albert, R.E., 1980) of the SAP position, concluded that there is substantial evidence for the mutagenicity of dimethoate, coupled with suggestive evidence for carcinogenicity in the 1973 Gibel study done on Wistar rats. The NCI bioassay involved a different strain of rats, namely, the Osborne-Mendel rat. In addition, the evidence of hematopietic toxicity in the Wistar rat but not in the Osbourne-Mendel rat indicates the possibility of a different metabolic handling of dimethoate or target organ susceptability in the two strains.

Therefore, the Agency has decided to retain the requirement for an oncogenic study on the Wistar rat at the highest dose level used in the Gibel study of 30 mg/kg given by stomach gavage twice a week.

b. Reproduction Testing--i. The Agency's Position of PD 2/3. The Agency did not propose any additional testing for reproductive effects in Position Document 2/3.

ii. Comments Indicating the Need for Additional Reproductive Studies. The Scientific Advisory Panel, in its formal comments, indicated that additional reproduction studies are necessary to assess the effect of dimethoate on male reproduction. The Panel stated that it noted positive effects in two studies on reproduction implying the possibility of effects on males. Therefore, the SAP suggested that the Agency require a reproductive test to determine dose-response effects on females (e.g. prevalence of pregnancy, pre and post implantation loss, survival and growth of young, etc.) and on males (e.g. spermatogenesis, seminal vesicle size, etc.).

iii. The Agency's PD 4 Response. The Agency rejects the Scientific Advisory Panel's recommendation since American Cyanamid's multigeneration reproduction study has shown no adverse effects in males. The Agency will not require additional reproduction testing but will require an additional teratogenicity study on technical dimethoate using 2 species of laboratory animals in accordance with proposed guidelines (FR 43, No. 163, Tuesday, August 22, 1978).

c. Mutagenicity Testing--i.. The Agency's Position in PD 2/3. In Position Document 2/3, the Agency concluded that additional data were required concerning the mutagenic potential of dimethoate. The data required included data concerning dimethoate's ability to cause gene mutation in animal cells; a dominant lethal study in mice; and spindle effects studies.

ii. Comments Requesting that the Spindle Effects Testing Requirement be Delected. American Cyanamid [7(30000/16c)] requested that the spindle effects testing requirement be deleted in the absence of guidelines.

iii. The Agency's PD 4 Response. The Agency rejects American Cyanamid's request to delete the requirement for spindle effects testing and will require these tests. The Agency is currently developing a policy for spindle effects and until that policy is available will provide advice and evaluate testing procedures for spindle effects.

iv. Comments Urging the Use of Mutagenicity Tests Presently Proposed in the Pesticide Registration Guidelines. American Cyanamid suggested that dimethoate be evaluated using mutagenicity tests presently proposed in the pesticide registration guidelines.

v. The Agency's PD 4 Response. The following studies represent only the minimum requirements for data on the potential heritable effects of Dimethoate. This is a subset of the studies proposed in the pesticide registration guidelines.

(1) A mammalian *in vitro* point mutation test.

(2) A sensitive sub-mammalian point mutation test. (Bacteria, fungi, insect).

(3) A primary DNA damage test (i.e., sister chromatid exchange or unscheduled DNA synthesis).

(4) A mammalian *in vitro* cytogenics test. If this suggests a positive result, a dominant lethal or heritable translocation test may be required.

After results from these test systems and other toxicology disciplines have been considered, additional testing may be required to further characterize or quantify the potential genetic risks.

Although the Agency's mutagenic testing requirements are not final, the standards for these test should be based on the principles set forth therein (FR 43, NO. 163, Tuesday, August 22, 1978). Protocols and choices of test systems should be accompanied by a scientific rationale. Substitutions of test systems for those listed above will be considered after discussion with the Agency.

The requirements should be considered an interim guide and not final Agency policy. However, the Agency does consider the above testing scheme to be a reasonable minimum requirement.

The Agency has established the mutagenic potential of dimethoate by means of the screening studies listed above and is now requiring additional testing to quantify risk to humans. The studies being required at this time are: 1) gene mutation study in mammalian system; 2) a dominant lethal study in mice; and 3) studies designed to detect spinde effects, i.e., an *in vivo* bone marrow cytogenetic study.

vi. *Comments Recommending that Mutagenic Assays be Conducted in Accordance with the SAP Recommendation on the Guidelines*. The Scientific Advisory Panel (SAP), in its formal comments, recommended that mutagenic assays be conducted in accordance with their recommendations on the guidelines, previously submitted to the Agency (May 31, 1978; Review of Proposed Rule Making on Subpart F, Guidelines for Registering Pesticides in the United States).

vii. The Agency's PD 4 Response. The Agency recognizes the fact that the final form of the guidelines has not been established yet. The Agency feels that, since the published reports on dimethoate, while not completely validated, have pointed up areas in which dimethoate could be a more potent mutagen than now indicated, the testing can be directed at specific aspects of mutagenicity.

The Agency is currently reviewing the SAP's recommendations on the Guidelines. Until the completion of this review, the mutagenic assays should be conducted in accordance with the Agency's proposed testing Guidelines where appropriate or by procedures recommended by consultation with the Agency.

viii. Comments Suggesting that the SAP Recommendations on Spindle Effects be Followed. The SAP suggested that the Agency follow their previously submitted recommendations on spindle effects (November 30, 1979; Review of FIFRA Section 6(6)(7) action on Benomyl and Thiophanate-methyl).

ix. The Agency's PD 4 Response. The Agency has recently completed guidelines on mutagenicity risk assessment. Those quidelines were published in the FEDERAL REGISTER on November 13, 19 0 (45 FR 74984). This document has considered earlier SAP comments in reaching a position on mutagenicity risk assessment (including spindle effects).

x. Comments on Using Bone Marrow Derived Cells in Spindle Effect Assays. The SAP recommended using bone marrow derived cells in spindle effect assays.

xi. The Agency's PD 4 Response. The Agency agrees that an *in vivo* bone marrow cytogenetic analysis may be of assistance, particularly since one of the unvalidated papers (Bhunya and Behera, 1975) indicated that dimethoate may affect chromosomes in bone marrow cells.

d. Delayed-Neurotoxicity Testing--i. The Agency's Position in PD 2/3. In Position Document 2/3, the Agency concluded that additional data were required concerning the potential of dimethoate to produce delayed neurotoxic effects.

ii. Comments Urging Re-evaluation of the Requirement for Another Delayed Neurotoxicity Study. The Scientific Advisory Panel (SAP), in its formal comments, recommended that the Agency re-evaluate the requirement for another delayed neurotoxicity study in light of a study by T.B. Gaines (1969).

iii. The Agency's PD 4 Response. The Agency has re-evaluated the American Cyanamid acute neurotoxicity study and the Gaines study. Since the dose in the American Cyanamid study was administered in feed instead of by gavage, the dose may not have been sufficiently large to determine dimethoate's neurotoxic potential.

The Gaines study, while indicating no neurotoxic effects of dimethoate, did not give important details, such as dosage used, number of animals used, and whether or not histopathology on the nerves was carried out. After reevaluating both the American Cyanamid (1965b) studies and the Gaines (1969 study the Agency concludes that not enough data is available in these studies to make a hazard determination.

Therefore, the Agency has decided to retain the requirement that a delayed neurotoxicity study be performed in accordance with EPA's proposed pesticide registration guidelines (FR 43, No. 163, Tuesday, August 22, 1978).

e. Applicator Exposure Studies--i. The Agency's Position in PD 2/3. In Position Document 2/3, the Agency concluded that additional exposure studies were needed to determine worker dermal and inhalation exposure during the application of dimethoate with air blast equipment.

ii. Comments on Additional Applicator Exposure Studies. No comments were received which objected to additional exposure studies of air blast applications. In fact several commenters, including SAP, Arizona [5(30000/16C)], California [8(30000/16c)], California Citrus Quality Council [9(30000/16c)], and Idaho [10(30000/16c)], recommended that the Agency support and consider research planned by the University of California on applicator exposure during air blast use on citrus.

iii. The Agency PD 4 Response. Additional field monitoring studies will be required to determine the exposure to applicators during application of dimethoate with air blast equipment and to determine the exposure to flaggers wearing protective clothing during aerial application.

Registrants are directed to conduct appropriate field studies to determine worker exposure (dermal and inhalation) during application of dimethoate using air blast type application equipment and flagger exposure (dermal and inhalation) during aerial application. Registrants shall gather such data for each crop where air blast equipment is used or on crops deemed representative of such applicator exposure situations, and also for aerial application. Registrants shall submit proposed test protocols for gathering applicator exposure data to the Agency with 90 days of receipt of the Agency 3(c)(2)(B) letter concerning dimethoate and shall complete all such tests and submit all exposure data to the Agency within eighteen (18) months of receipt of the Agency's 3(c)(2)(B) letter for dimethoate. The Agency's 3(c)(2)(B) letter setting forth additional testing requirements for dimethoate will be issued shortly after publication of the Agency's final Notice of Determination for dimethoate.

The exposure study currently underway at the University of California (Riverside) may satisfy part of this requirement for air blast equipment. Therefore, data from that study should be submitted to the Agency as soon as possible following the conclusions of the study.

III. CONCLUSIONS

After reviewing comments from the Secretary of Agriculture, the Scientific Advisory Panel, and others who commented on EPA's findings and recommendations concerning dimethoate as set forth in PD 2/3, the Agency has decided to implement the Proposed Regulatory Option as put forward in PD 2/3 and restated in Chapter I of this document with the following modifications:

(1) The Agency will not cancel the air blast application of dimethoate on citrus, pome fruits, and pecans. However, the Agency will require an exposure study of dimethoate applicators using contemporary air blast equipment to allow a better assessment, than is currently available, of the applicators' potential risk from dimethoate in air blast use situations. After the results from the exposure studies become available, the Agency will reevaluate air blast application of dimethoate.

(2) The Agency will not require a label change to require automatic flagging. Instead the following label statement will be required on all products intended for aerial application:

> Automatic flagging devices should be used whenever feasible.
> If Human Flaggers are employed they must wear the protective clothing and respirator specified on this label.

In addition, the Agency will review an exposure study of flaggers wearing protective clothing during the aerial application of dimethoate to allow a better assessment of the flaggers' potential risk from dimethoate in the aerial use situation.

(3) The Agency will exempt pilots from the protective clothing and equipment requirement when flying the aircraft.

(4) The Agency will not require the label warning statement for female applicators. However, the Agency will require an additional teratology study on technical dimethoate.

The Agency's final determination for dimethoate is as follows.

A. Regulatory Actions

1. Unconditional denial of all applications for registration of dimethoate products for use in dust formulations.

2. Cancellation and denial of registrations of dimethoate products for all uses, unless the registrants or applicants for registration modify the labeling of dimethoate products to include the following:

> Required Clothing and Equipment for Application
>
> All applicators, including homeowners and flaggers, and all personnel involved with the mixing, loading, and transferring operations, must wear the protective

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clothing and equipment enumerated below. Pilots are exempt from this requirement. The protective clothing and equipment to be worn is as follows:

a. Impermeable gloves (for example, rubber or plastic covered gloves).

b. Rubber or synthetic rubber boots or boot covers.

c. Long-sleeved shirt and long pants made of closely woven fabric.

d. Wide-brimmed hat.

e. Respirators must be worn by flaggers and mixer/loaders.

3. Cancellation and denial of registration of dimethoate products labeled for aerial application unless the registrants or applicants for registration modify the terms and conditions of registration to include the following statements:

AUTOMATIC FLAGGING DEVICES SHOULD BE USED WHENEVER FEASIBLE

IF HUMAN FLAGGERS ARE EMPLOYED THEY MUST WEAR THE PROTECTIVE CLOTHING AND RESPIRATOR SPECIFIED ON THIS LABEL.

In addition to these actions, the Agency has determined, under the authority of section 3(c)(2)(B), that additional data are required to maintain the registrations of dimethoate products in effe . The request for this data is independent of the Agency's terminations regarding the termination of this RPAR. Henc the 3(c)(2)(B) data requirements cannot be contested in administrative hearing challenging the terms of a cance ation notice. The additional studies which the Agency s requiring are summarized below.

B. Testing Requirements

1. A dimeth te oncogenicity study using the same strains of mice d rats used by Gibel et al. (1973). The proposed prot col for this study must be submitted within 90 days of receipt of the Agency's 3(c)(2)(B) letter concerning dimeth ate. This study must be completed within three years of re eipt of the Agency's 3(c)(2)(B) letter concerning dimeth ate (PD4).

2. Mutagenic ty tests, including gene mutation studies in mammalian syst ms, a dominant lethal study in mice, and studies designed o detect spindle effects, i.e., an *in vivo* bone marrow cytog netic study. The protocol for these studies must be s mitted within 90 days of receipt of the Agency's 3(c)(2)( ) letter concerning dimethoate. These tests must be com leted and submitted within eighteen months of receipt of the Agency's 3(c)(2)(B) letter concerning dimethoate.

3. Delayed n urotoxicity tests which must be conducted, in accordance wit EPA's proposed pesticide registration

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guidelines. The protocol for these tests must be submitted within 90 days of receipt of the Agency's 3(c)(2)(B) letter concerning dimethoate. These tests must be completed within eighteen months of receipt of the Agency's 3(c)(2)(B) letter concerning dimethoate.

4. Teratology tests on the technical dimethoate using 2 species of laboratory animals in accordance with the proposed registration guidelines published in the FEDERAL REGISTER of August 22, 1978 (43 FR 37336). The protocol for these tests must be submitted within 90 days of receipt of the Agency's 3(c)(2)(B) letter concerning dimethoate. These tests must be completed within eighteen months of receipt of the Agency's 3(c)(2)(B) letter concerning dimethoate.

5. Exposure studies to determine worker dermal and inhalation exposure during the application of dimethoate with air blast equipment and dermal and inhalation exposure for flaggers during aerial application of dimethoate. Exposure data must be gathered for each crop where air blast equipment is used or on crops deemed representative of such applicator exposure situations. Registrants and applicants must submit proposed test protocols for gathering applicator exposure data within 90 days of receipt of the Agency's 3(c)(2)(B) letter and must complete all such tests and submit all exposure data within eighteen months of receipt of the Agency's 3(c)(2)(B) letter for dimethoate The

Agency will reevaluate air blast application of dimethoate after the results of the exposure studies become available.

The Agency's 3(c)(2)(B) letter for dimethaote will be issued shortly after publication of the Agency's final Notice of Determination for dimethoate.

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The documents cited in this bibliography, as well as other documents which make up the Administrative Record for the Agency's actions on dimethoate, are available for inspection on normal working days between the hours of 8 a.m. to 4.30 p.m. in the offices of the Special Pesticide

Review Division, 1921 Jefferson Davis Highway, Crystal Mall Building #2, Room 720, Arlington, Virginia 22202.

Dated: 1/6/81

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